SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Verapamil 40mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Verapamil Hydrochloride 40mg/5ml

Excipients with known effect:

Propylene glycol (E1520): 500mg/5ml
Liquid Maltitol (E965): 2500mg/5ml
Ethanol: 2.1mg/5ml
Benzoic acid (E210): 5mg/5ml

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Oral Solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. Treatment of mild to moderate hypertension.

2. Treatment and prophylaxis of chronic stable angina, vasospastic angina and unstable angina.

3. Treatment and prophylaxis of paroxysmal supraventricular tachycardia and the reduction of ventricular rate in atrial flutter/fibrillation. Verapamil should not be used when atrial flutter/fibrillation complicates Wolff-Parkinson-White syndrome (see Contraindications).

4.2 Posology and method of administration

Hypertension: Initially 120mg b.d. increasing to 160mg b.d. when necessary. In some cases, dosages of up to 480mg daily, in divided doses, have been used. A further reduction in blood pressure may be obtained by combining verapamil with other antihypertensive agents, in particular diuretics. For concomitant administration with beta-blockers see Precautions.

Angina: 120mg t.d.s. is recommended. 80mg t.d.s. can be completely satisfactory in some patients with angina of effort. Less than 120mg t.d.s is not likely to be effective in variant angina.

Supraventricular tachycardias: 40-120mg, t.d.s. according to the severity of the condition.

Hepatic Impairment: Verapamil is extensively metabolised in liver and for those patients with impaired liver function, the dose should be reduced and carefully titrated.

Renal Impairment: About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Verapamil should be prescribed cautiously when renal function is impaired. Careful patient monitoring is recommended.

Children:

Up to 2 years: 20mg, 2-3 times a day.

2 years and above: 40-120mg, 2-3 times a day, according to age and effectiveness.

Elderly:

The adult dose is recommended unless liver or renal function is impaired (see Precautions).

4.3 Contraindications

Hypersensitivity to verapamil or any of the 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 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 Intravenous dantrolene (See section 4.5)
Hypotension of less than 90mm Hg systolic
Atrial flutter or fibrillation associated with an accessory pathway (e.g. Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndrome) may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.

Porphyria
Combination with ivabradine (see section Interactions with other medicinal products and other forms of interaction).
Concomitant ingestion of grapefruit juice.

4.4 Special warnings and precautions for use

Since verapamil is extensively metabolised in the liver, careful dose titration of verapamil 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).

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 incipient cardiac failure, therefore, verapamil should be given only after such cardiac failure has been controlled with appropriate therapy, e.g. digitalis.

When treating hypertension with verapamil, monitoring of the patient’s blood pressure at regular intervals is required.

Verapamil is extensively metabolised in the liver and special care should be taken in cases where liver damage exists, as plasma levels of verapamil may be increased (see section 4.2)

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 on the lowest possible dose of verapamil and titrated upwards. If verapamil treatment is to be added to patients already

taking HMG CoA reductase inhibitor (e.g. simvastatin, atorvastatin or lovastatin), refer to the 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).

Excipient warnings

This product contains:

- Propylene glycol (E1520). This medicine contains 500mg propylene glycol in each 5ml dose. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old. While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.
  Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.
- Liquid Maltitol (E965). Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Ethanol. This medicine contains 2.1mg of alcohol (ethanol) in each 5ml dose. The amount in 5ml of this medicine is equivalent to less than 1ml beer or 1ml wine. The small amounts of alcohol in this medicine will not have any noticeable effects.
- Benzoic acid (E210). This medicine contains 5mg benzoic acid in each 5ml dose.
- Sodium. This medicine contains less than 1mmol sodium (23mg) per 5ml dose, that is to say essentially ‘sodium free’.

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 metabolised 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 (such as ketoconazole, erythromycin and ritonavir) 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 may increase the risk of bleeding.

Alcohol: Plasma concentration may be increased (see section 4.7).

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).

Anticoagulants: When oral verapamil was co-administered with dabigatran etexilate (150 mg), 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 240 mg 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.

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).

Anticonvulsants: Verapamil may increase the plasma concentrations of carbamazepine. This may produce side effects such as diplopia, headache, ataxia or dizziness. Levels of verapamil may be reduced when taken with phenytoin.

Antidepressants: Verapamil may increase the plasma concentrations of imipramine.

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

Antihypertensives, diuretics, vasodilators: Potentiation of the hypotensive effect.

Anti-infectives: Rifampicin may reduce the plasma concentration of verapamil which may produce a reduced blood pressure lowering effect. 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 under treatment with verapamil.

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

Cimetidine: Increase in verapamil serum level is possible.

Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter, Pglycoprotein (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.

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.

HMG Co-A Reductase Inhibitors (Statins): Verapamil may increase the plasma concentrations of simvastatin, atorvastatin and lovastatin.

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 re-titrate against serum cholesterol concentrations.

Atorvastatin has been shown to increase verapamil levels. Although there is no direct in vivo clinical evidence, there is a 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 metabolised by CYP 3A4 and are less likely to interact with verapamil.

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).

Intravenous dantrolene: The association of this muscle relaxant given intravenously and verapamil is potentially dangerous (can cause fatal ventricular fibrillation in animals) and is contraindicated.

Lithium: Serum levels of lithium may be reduced (pharmacokinetic effect); 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. The effects of verapamil may be additive to other hypotensive agents.

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.

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.

Co-administration of verapamil with metformin may reduce the efficacy of metformin.

4.6 Fertility, Pregnancy and lactation

Pregnancy
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.

Lactation
Verapamil is excreted into the breast milk in small amounts and is unlikely to be harmful. However, rare hypersensitivity reactions have been reported with verapamil and, therefore, it should only be used during lactation if, in the clinician's judgement, it is essential for the welfare of the patient.

Fertility
No information is available regarding the effects of verapamil on fertility.

4.7 Effects on ability to drive and use machines

Depending on individual susceptibility, the patient's ability to drive a vehicle or operate machinery or work under hazardous conditions may be impaired. This is particularly true in the initial stages of treatment, or when changing over from another medication. 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

Verapamil is generally well tolerated. Side effects are usually mild and transient and discontinuation of therapy is rarely necessary.

Immune System Disorders: Allergic reactions (e.g. erythema, pruritus, urticaria) are very rarely seen.

Nervous System Disorders: Tremor and extrapyramidal syndrome. Headaches and dizziness have been reported rarely. Paraesthesia may occur.

Ear and Labyrinth Disorders: Vertigo and tinnitus.

Cardiac Disorders: Particularly when given in high doses or in the presence of previous myocardial damage, some cardiovascular effects of verapamil may occasionally be greater than therapeutically desired: bradycardic arrhythmias, such as sinus bradycardia, sinus arrest with asystole, second and third degree AV block, bradyarrhythmia in atrial fibrillation, palpitations, tachycardia, development or aggravation of heart failure.

Vascular Disorders: Peripheral oedema, hypotension. Flushing is observed occasionally. Erythromelalgia may occur.

Gastrointestinal Disorders: Constipation may occur. Nausea, vomiting, ileus, abdominal pain/discomfort have been reported rarely.
Gingival hyperplasia may very rarely occur when the drug is administered over prolonged periods, and is fully reversible when the drug is discontinued.

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

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

Musculoskeletal and Connective Tissue Disorders: In very rare cases, there may be 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. Rises in prolactin levels have been reported.

General Disorders and Administration Site Conditions: Fatigue and ankle oedema have been reported rarely.

Investigations: 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 Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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: blood pressure fall (at times to values not detectable), shock symptoms, 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, sinus bradycardia, sinus arrest hyperglycaemia, stupor and metabolic acidosis, acute respiratory distress syndrome. Fatalities have occurred as a result of overdose. 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. Gastric lavage, taking the usual precautionary measures may be appropriate even later than 12 hours after ingestion, if no gastrointestinal motility (peristaltic sounds) is detectable.

The usual intensive resuscitation measures, 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 – 20ml of a 10% calcium gluconate solution administered intravenously (2.25 – 4.5mmol), repeated if necessary or given as a continuous drip infusion (e.g. 5mmol/hour).

The following measures may also be necessary: In case of second and third degree AV block, sinus bradycardia, asystole: atropine, isoprenaline, orciprenaline or pacemaker therapy. In case of hypotension after appropriate positioning of the patient: dopamine, dobutamine, noradrenaline. If there are signs of continuing myocardial failure: dopamine, dobutamine, cardiac glycosides or if necessary, repeated calcium gluconate injections.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 the cells of the intracardiac conduction system. Verapamil lowers peripheral vascular resistance with no reflex tachycardia. Its efficacy in reducing both raised systolic and diastolic blood pressure is thought to be due to this mode of action. The decrease in systemic and coronary vascular resistance and the sparing effect on intracellular oxygen consumption appear to explain the anti-anginal properties of the drug. 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

Absorption
Over 90% of verapamil is absorbed following administration with peak plasma concentrations occurring between 1 and 2 hours and does not appear to be affected markedly by food.

Distribution, biotransformation and elimination
Verapamil is subject to pre-systemic hepatic metabolism with up to 80% of the dose eliminated this way. Because of rapid biotransformation of verapamil during its first pass through the portal circulation, absolute bioavailability ranges from 20 – 35%. Verapamil is widely distributed throughout the body with a distribution half-life of 15 – 30 mins. Verapamil is 90% bound to plasma proteins, mainly to albumin and 1 glycoprotein. The half life of verapamil after a single oral dose is between 2 and 7h. However, after repeated administration it increases to 4.5 to 12h resulting in accumulation of the drug.

Elderly
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 impairment
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 impairment
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

Verapamil is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol, benzoic acid, liquid maltitol, dill water concentrate (contains ethanol), liquorice flavour, citric acid monohydrate, sodium citrate and purified water.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months
3 months once open

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Bottle: Amber (Type III) glass
Closure: HDPE, EPE wadded, tamper evident, child resistant closure.
Pack Size: 150ml

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Essential Pharma Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 41871/0021

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10 DATE OF REVISION OF THE TEXT

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