Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Verisop 80 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 80 mg of Verapamil hydrochloride.
Each tablet contains 80 mg lactose (anhydrous).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

Round, white, biconvex, film-coated tablets, marked 'VL' b/l '80' on one face and 'G' on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Verapamil is indicated in the prophylaxis, and/or treatment of:

- Angina pectoris, including Prinzmetal's angina (coronary spasm, vasospastic angina).
- Supraventricular tachycardias such as paroxysmal supraventricular tachycardia, atrial fibrillation/flutter with rapid ventricular response (except in WPW syndrome, see Section 4.3, Contraindications).
- Mild to moderate essential hypertension.

4.2 Posology and method of administration

Verisop 80mg is for oral use.
Verapamil should not be taken with grapefruit juice (see section 4.5, Interactions).
Verisop tablets should be taken with or shortly after meals together with some liquid.

Adults Only:
Angina, including Prinzmetal's angina
120 mg, 3-4 times daily. Although 80 mg 3 times daily may be adequate in many patients with angina of effort, doses below 120 mg 3 times a day are unlikely to be effective in angina at rest and Prinzmetal's angina.

Supraventricular tachycardia
40 mg - 120 mg 3-4 times daily according to the severity of the condition.

Essential Hypertension
40 mg - 120 mg 3-4 times daily. In long-term treatment, a daily dose of 480 mg should not be exceeded; short-term dose increases are possible only when directed by the physician.

4.3 Contraindications

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

2. Cardiovascular shock, complicated acute myocardial infarction (bradycardia, hypotension, left ventricular failure), severe conduction disorders (second and third degree AV block, sino-atrial block).

3. Sick-sinus syndrome (bradycardia-tachycardia syndrome).

4. Manifest heart failure.

5. Atrial fibrillation/flutter with simultaneous pre-excitation syndrome, e.g. WPW syndrome (risk of provoking ventricular tachycardia).

6. Use in pregnancy unless considered essential by the physician.

7. Simultaneous intravenous administration of ß-adrenoceptor blocking agents.

8. Combination with ivabradine (see section 4.5).

4.4 Special warnings and precautions for use

1. Verapamil reduces blood pressure, care should be exercised in patients already on anti-hypertensive therapy, or with impaired renal function.

2. Patients with heart failure or those who are susceptible to heart failure should be fully digitalised before verapamil therapy as it may aggravate or precipitate cardiac failure.

3. Verapamil should be used with extreme caution in patients with first degree AV block, bradycardia < 50 beats/min, hypotension < 90 mmHg systolic and ventricular tachycardias (QRS complex ≥ 0.12 sec).

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

5. In patients with impaired hepatic function, the effect of verapamil is intensified and prolonged, depending on the severity of the liver disease, due to diminished drug metabolism. In these patients dosage intervals should be prolonged and low doses used.

6. If acute cardiovascular side effects arise, treat as for overdose (see Section 4.9, Overdose).

7. Colchicine: There has been a single postmarketing 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. (See Section 4.5, Drug Interactions).

8. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

The following table provides a list of potential drug interactions with verapamil:

Potential Drug Interactions associated with Verapamil

Concomitant drug	**Potential effect on verapamil or concomitant drug**	**Comment**
Alpha blockers		
Prazosin	↑ prazosin Cmax (~40%) with no effect on half-life	Additional information follows
Terazosin	↑ terazosin AUC (~24%) and Cmax (~25%)	
Antiarrhythmics		
Flecainide	Minimal affect on flecainide plasma clearance (<~10%); no effect on verapamil plasma clearance	Additional information follows
Quinidine	↓ oral quinidine clearance (~35%)	
Antiasthmatics		
Theophylline	↓ oral and systemic CL by ~20%	Reduction of CL was lessened in smokers (~11%)
Anticonvulsants		
Carbamazepine	↑ carbamazepine AUC (~46%) in refractory partial epilepsy patients	Additional information follows
Antidepressants		
Imipramine	↑ imipramine AUC (~15%)	No effect on level of active metabolite, desipramine
Antidiabetics		
Glyburide	↑ glyburide Cmax (~28%), AUC (~26%)	
Anti-gout agents		
Colchicine	Possible ↑ colchicine levels	Additional information follows
Anti-infectives		
Erythromycin	Possible ↑ in verapamil levels	
Rifampin	↓ verapamil AUC (~97%), Cmax (~94%), oral bioavailability (~92%)	Additional information follows
Telithromycin	Possible ↑in verapamil levels	
Antineoplastics		
Doxorubicin	↑ doxorubicin AUC (89%) and Cmax (61%) with oral verapamil administration	In patients with small cell lung cancer
	No significant change in doxorubicin PK with intravenous verapamil administration	In patients with advanced neoplasms
Barbiturates		
Phenobarbital	↑ oral verapamil clearance	

	(~5-fold)	
Benzodiazepines and other anxiolytics		
Buspirone	↑ buspirone AUC, Cmax by ~3.4-fold	
Midazolam	↑ midazolam AUC (~3-fold) and Cmax (~2-fold)	
Beta blockers		
Metoprolol	↑ metoprolol AUC (~32.5%) and Cmax (~41%) in angina patients	Additional information follows
Propranolol	↑ propranolol AUC (~65%) and Cmax (~94%) in angina patients	
Cardiac glycosides		
Digitoxin	↓ digitoxin total body clearance (~27%) and extrarenal clearance (~29%)	
Digoxin	Healthy subjects: ↑ Cmax by ~45-53% ↑ Css by ~42% and ↑ AUC by ~52%	
H2 Receptor antagonists		
Cimetidine	↑ AUC of R- (~25%) and S- (~40%) verapamil with corresponding ↓ in R-and S-verapamil clearance	
Immunologics		
Ciclosporin	↑ ciclosporin AUC, Css, Cmax by ~45%	
Everolimus	Possible ↑ everolimus levels	
Sirolimus	Possible ↑ sirolimus levels	
Tacrolimus	Possible ↑ tacrolimus levels	
Lipid lowering agents		
Atorvastatin	Possible ↑ atorvastatin levels Increase verapamil AUC (~42.8%)	Additional information follows
Lovastatin	Possible ↑ lovastatin levels	
Simvastatin	↑ simvastatin AUC (~2.6-fold), Cmax (~4.6-fold)	
Serotonin receptor antagonists		
Almotriptan	↑ almotriptan AUC (~20%) ↑ Cmax (~24%)	
Uricosurics		
Sulfinpyrazone	↑ verapamil oral clearance (~3-fold) ↓ bioavailability (~60%)	Additional information follows

Other		
Grapefruit juice	↑ R- (~49%) and S- (~37%) verapamil AUC ↑ R- (~75%) and S- (~51%) verapamil Cmax	Elimination half life and renal clearance not affected
St.John's Wort	↓ R- (~78%) and S- (~80%) verapamil AUC with corresponding reductions in Cmax	

Other Drug Interactions and Additional Drug Interaction Information

Colchicine: Colchicine is a substrate for both CYP3A and the efflux transporter, P-gp. Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicine are administered together, the potential inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine. (See Section 4.4, Special Warnings and Special Precautions for Use).

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).

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

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 dose of verapamil may be decreased.

Quinidine: hypotension. Pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy.

Carbamazepine: increased carbamazepine levels. This may produce carbamazepine side effects such as diplopia, headache, ataxia or dizziness.

Lithium: increased lithium neurotoxicity.

Rifampin: blood pressure lowering effect may be reduced.

Sulfinpyrazone: Blood pressure lowering effect may be reduced.

Neuromuscular blockers: the effect of neuromuscular blocking agents may be potentiated.

Aspirin: increased tendency to bleed.

Ethanol (alcohol): Elevation of ethanol plasma levels.

HMG Co-A Reductase Inhibitors ("Statins"): 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.

Simvastatin: Risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil and simvastatin in high doses.

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

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

4.6 Fertility, pregnancy and lactation

During pregnancy (especially in the first trimester) and lactation, Verisop should only be used if considered essential by the physician.

4.7 Effects on ability to drive and use machines

In some patients, verapamil may impair the ability to drive or operate machinery. This is more likely to occur at the start of treatment and if alcohol has been consumed.

4.8 Undesirable effects

Cardiac disorders
Particularly when given in high doses or in the presence of previous damage, some cardiovascular effects of verapamil may occasionally be greater than therapeutically desired: bradycardic arrhythmias (sinus bradycardia, sinus arrest with asystole, 1st, 2nd or 3rd degree AV block or bradyarrythmia in atrial fibrillation), tachycardia, palpitations, hypotension, development or aggravation of heart failure.

Nervous system disorders
Vertigo, dizziness, headache, fatigue, tremor, nervousness, tinnitus and extrapyramidal syndrome have been reported.

Gastrointestinal disorders
Constipation has been reported frequently. Nausea, vomiting ileus and abdominal pain/discomfort has also been reported. On rare occasions, gingival hyperplasia, which is fully reversible when the drug is discontinued, may occur under long-term treatment.

Skin and subcutaneous tissue disorders
Hypersensitivity has been reported following treatment. Exanthema, pruritus, urticaria, erythema, purpura, Quincke's oedema and Stevens-Johnson syndrome, erythema multiforme and alopecia have been reported. In rare cases, erythromelalgia and paraesthesia may occur.

Musculoskeletal and connective tissue disorders
In very rare cases, there may be muscular weakness or myalgia and arthralgia.

Endocrine disorders
In very rare cases, gynaecomastia has been observed, which is fully reversible following discontinuation of treatment. Rises in prolactin levels have been reported and isolated cases of galactorrhoea.

Vascular disorders
Vasodilation may result in flushing, headache and peripheral oedema.

Hepatobiliary disorders
A reversible increase in transaminases and/or alkaline phosphatase, which is probably a sign of allergic hepatitis, has also been reported.

Reproductive system and breast disorders
Impotence has been rarely 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 1 6764971; Fax:

+353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The usual intensive care measures should be taken. Fatalities have occurred as a result of overdose. Verapamil hydrochloride cannot be removed by haemodialysis.

The specific antidote is calcium, e.g. 10-20 ml in 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 the case of 2nd and 3rd degree AV block, sinus bradycardia, asystole: Atropine, isoprenaline, orciprenaline or pacemaker therapy.

In the case of hypotension: Dopamine, dobutamine, norepinephrine.

If there are any signs of continuing myocardial failure: Dopamine, dobutamine, if necessary repeated calcium injections, and possibly other medication that increases cardiac contractility combined with isoprenaline.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives
ATC code: C08DA01

Verapamil inhibits the transmembrane influx of calcium ions into the heart and vascular smooth muscle cell. The myocardial oxygen demand is lowered directly as a result of the effect on the energy consuming metabolic processes of the myocardial cell and indirectly due to a reduction of the afterload.

Due to its effect on coronary vascular smooth muscle, Verisop enhances myocardial blood flow, even in post-stenotic areas, and relieves coronary spasms.

These properties contribute to the anti-ischaemic and antianginal efficacy of Verisop in all types of coronary artery disease.

Verisop has a marked antiarrhythmic effect, particularly in supravetricular arrhythmias. It delays impulse conduction in the AV node. Owing to this, sinus rhythm is restored and/or ventricular rate is normalised, depending on the type of arrhythmia. Normally, the rate is either not affected or only minimally lowered.

The antihypertensive effect of Verisop stems from a decrease in peripheral vascular resistance, without an increase in heart rate as a reflex response. As early as day 1 of treatment, blood pressure falls; the effect is found to persist also in long-term therapy.

5.2 Pharmacokinetic properties

Verapamil is absorbed rapidly and almost exclusively in the small intestine. The absorption rate is 90-92%. Half-life values between 3 and 7 hours have been measured for the elimination of unchanged substance from the plasma after single intravenous and oral administration. On multiple administration, the half-life of verapamil can be prolonged to about double the value measured after single administration. Peak verapamil hydrochloride plasma levels are reached one or two hours after IR administration.

Verapamil is metabolised almost completely. The main metabolites are norverapamil and the primary and secondary amines.

In animal studies, only norverapamil showed any appreciable pharmacological activity, while the other metabolites were practically ineffective.

Verapamil and its metabolites are excreted primarily in the urine; only 3 to 4% is excreted as unchanged drug. Within 24 hours 50%, within 48 hours 55-60% and within 5 days 70% of the administered dose is excreted in the urine. Up to 16% is excreted in the faeces. Recent findings have shown that there are no differences between the pharmacokinetics of verapamil in persons with healthy kidneys and in patients with terminal renal failure.

In coronary heart disease and hypertension, no correlation was found between the therapeutic effect and the plasma concentration; a definite correlation with the plasma level was determined only for the effect on the PR interval. The concentration curve of verapamil in the plasma is protracted after administration of the sustained-release formulations, and is also flatter and more homogenous than after administration of the instant release formulations. Plasma protein binding is about 90%.

Transfer across the placenta: Verapamil passes the placental barrier; the concentration in the plasma of the umbilical vein blood was between 20 and 92% of the plasma concentration of the mother.

Transfer into human milk: Although verapamil is excreted in human milk, the concentrations are so low at therapeutic dose levels that no appreciable pharmacological effect is to be expected in infants.

5.3 Preclinical safety data

The cardiovascular findings and the diffuse gingival hyperplasia seen in the chronic toxicity of verapamil hydrochloride are taken into account in Section 4.8, Undesirable Effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Lactose anhydrous
Microcrystalline cellulose
Pregelatinized maize starch
Sodium starch glycollate
Purified talc
Magnesium stearate

Film Coating

Hypromellose
Diethyl phthalate
Carnauba Wax
Opadry White Y-1-7000 containing:
Titanium dioxide E171
Macrogol 400
Hypromellose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polypropylene securitainers with polyethylene caps containing 100, 250, 500 and 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited
12 Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0405/020/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 13 April 2008

10 DATE OF REVISION OF THE TEXT

June 2016