SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vera-Til SR 120mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 120 mg Verapamil hydrochloride.
Excipient with known effect: Each tablet contains 3.56 mg of lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Modified release film coated tablet
Round, beige to ochre, biconvex, with score on one side, approximate diameter 11mm.

The score line is not intended for breaking the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vera-Til SR is indicated for:
The treatment of mild to moderate hypertension.
The treatment and prophylaxis of angina pectoris.

Secondary prevention of re-infarction after an acute myocardial infarction in patients without heart failure, and not receiving diuretics (apart from low-dose diuretics when used for indications other than heart failure), and where beta-blockers are not appropriate. Treatment is to be started at least one week after an acute myocardial infarction.

4.2 Posology and method of administration

Posology
Adults

**Hypertension:** The usual dose is one tablet of Vera-Til SR 240 mg daily. For patients new to verapamil therapy the doctor should consider halving the dose to one Vera-Til SR 120 mg tablet daily. Most patients respond to 240 mg daily given as a single dose. If control is not achieved within at least one week the dosage may be increased to a maximum of two Vera-Til SR 240 mg tablets daily (one taken in the morning and one in the evening at an interval of about 12 hours). Other anti-hypertensive agents, in particular diuretics, may be used in combination with Vera-Til SR 240 mg tablets to achieve further reduction in blood pressure. Vera-Til SR 120 mg tablets may be used for dose titration purpose.

**Angina pectoris:** The usual dose is one tablet of Vera-Til SR 240 mg twice daily. A small number of patients respond to a lower dose and where indicated, adjustment down to one Vera-Til SR 240 mg tablet daily could be made. Vera-Til SR 120 mg tablets may be used for dose titration purposes.

**Secondary prevention of re-infarction after an acute myocardial infarction in patients without heart failure, and not receiving diuretics (apart from low-dose diuretics when used for indications other than heart failure), and where beta-blockers are not appropriate:** Treatment is to be started at least one week after an acute myocardial infarction. 360 mg/day in divided doses, to be taken either as 120 mg three times daily, or as 240 mg to be taken in the morning and 120 mg to be taken in the evening, on a daily basis.

**Elderly patients**

The adult dose is recommended, except in patients with impaired liver or renal function or cardiac conduction problems, where a reduced dosage may be necessary (see section 4.4).

Verapamil therapy should be discontinued gradually after long-term treatment.

**Paediatric population**

The safety and efficacy of Vera-Til SR tablets in children and adolescents have not been established. No data are available. Vera-Til SR tablets are not recommended for children and adolescents.

**Method of administration**

For oral use only. Vera-Til SR tablets should not be chewed. Vera-Til SR Tablets 120 mg are to be swallowed whole with some liquid.

### 4.3 Contraindications

Hypersensitivity to the active substance or to 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 (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.

Patients with atrial fibrillation/flutter with simultaneously existing of an accessory pathway e.g. Wolff-Parkinson-White syndrome, may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.

Combination with ivabradine (see section 4.5).

4.4 Special warnings and precautions for use

Verapamil may affect impulse conduction and therefore should be used with caution in patients with bradycardia or first degree AV block. Verapamil may affect left ventricular contractility; this effect is small and often 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.

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).

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

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

Patient with renal impairment
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.

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 CYP2C19. 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 are potential drug interactions associated with verapamil:

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

**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 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. However, there may be increased sensitivity to lithium causing enhanced neurotoxicity.

**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 concentrations of theophylline.

**Uricosurics**
Sulfinpyrazone may reduce the plasma concentrations of verapamil which may produce a reduced blood pressure lowering effect.

**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.

**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

**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.

**Breast-feeding**
Verapamil is excreted into the 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 and rarely hypersensitivity reactions in nursing infants with verapamil, it should only be used during lactation if, in the clinician’s judgement, 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 or 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 medication or when the dose is raised. 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 Postmarketing Surveillance or Phase IV Clinical Trials

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

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

**Nervous system disorders:** headache, dizziness, paresthesia, tremor and extrapyramidal syndrome.

**Ear and labyrinth disorders:** vertigo and tinnitus.

**Cardiac disorders/vascular disorders:** bradycardic arrhythmias such as sinus bradycardia, sinus arrest with asystole, 2nd and 3rd degree AV block, bradyarrhythmia in atrial fibrillation, peripheral oedema, palpitations, tachycardia, development or aggravation of heart failure and hypotension. There have been rare reports of flushing.

**Gastrointestinal disorders:** nausea, vomiting, constipation, ileus and abdominal pain/discomfort. Gingival hyperplasia may occur very rarely 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.

**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, and is fully reversible in all cases when the drug was discontinued.

**General disorders and administration site conditions:** fatigue.

**Investigations:** A reversible impairment of liver function characterized by an increase of transaminase and/or alkaline phosphatase may occur on very rare occasions during verapamil treatment and is most probably a hypersensitivity reaction. Rises in blood prolactin levels have been reported.
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: blood pressure drop (at times to values not detectable), shock symptoms, loss of consciousness, 1st and 2nd degree AV block (frequently as Wenkebach’s phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm, asystole, sinus bradycardia up to high degree AV block, 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 intoxication with large amounts of slow release preparations such as Vera-Til SR 240 mg tablets, 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 gastro-intestinal 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 Verapamil 240 mg and 120 mg 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

If there are signs of continuing myocardial failure: dopamine, dobutamine, if necessary repeated calcium injections.
5.1 Pharmacodynamic properties

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

ATC code: C08DA01

**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 metabolized. Norverapamil is one of 12 metabolites identified in urine, has 10 to 20% of the pharmacologic activity of verapamil and accounts for 6% of excreted drug. The steady-state plasma concentrations of norverapamil and verapamil are similar.

Steady state after multiple once daily dosing is reached after three to four days.

**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%.
Metabolism
Verapamil is extensively metabolized. In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver, with 12 metabolites having been identified, most in only trace amounts. The major metabolites have been identified as various N and O-dealkylated products of verapamil. Of these metabolites, only norverapamil has any appreciable pharmacological effect (approximately 20% that of the parent compound), which was observed in a study with dogs.

Elimination
Following 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

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 insufficiency:
Impaired renal function has no effect on verapamil pharmacokinetics, as shown by comparative studies in patients with end-stage renal failure and subjects with healthy kidneys. Verapamil and norverapamil are not significantly removed by hemodialysis.

Hepatic insufficiency:
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
A long-term toxicological study in rats gave no evidence that verapamil has any tumorigenic potential. In vitro and in vivo studies have shown that verapamil does not exert any mutagenic effects. Embryotoxic studies in rabbits and rats at daily doses of up to 15mg/kg and 60mg/kg respectively gave no evidence of teratogenic potential. However, embryotoxic effects were observed in rats at this dosage level, which already proved toxic for the maternal animals.
6  PHARMACEUTICAL PARTICULARS

6.1  List of excipients

Core:
- Sodium alginate 80cP x H₂O
- Microcrystalline cellulose 90μm
- Povidone
- Magnesium stearate
- Colloidal anhydrous silica

Film-coating:
- Yellow ferric oxide (E172)
- Opadry, white:
- Lactose monohydrate
- Hypromellose
- Titanium dioxide (E171)
- Macrogol 4000

6.2  Incompatibilities

Not applicable

6.3  Shelf life

4 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

PVDC / PVC or Polypropylene/aluminium foil blister strips packed into cardboard cartons of 28, 30, 56 and 100 tablets. Not all pack sizes may be marketed.

6.6  Special precautions for disposal and other handling

No special requirements.

7.  MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
220 Butterfield, Great Marlings,
8 MARKETING AUTHORISATION NUMBER
PL 11311/0077

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 September 2001
Date of latest renewal: 31 March 2009

10 DATE OF REVISION OF THE TEXT

30/01/2018