SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Verapamil 120 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 120 mg of verapamil hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets
Biconvex, film-coated tablets engraved 3T1 or 120/0241 and plain on the reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Verapamil is indicated for the treatment and prophylaxis of angina pectoris. It may be used in the treatment and prophylaxis of paroxysmal supraventricular tachycardia, atrial fibrillation and atrial flutter; (verapamil should not be used where atrial flutter/fibrillation complicates Wolff-Parkinson-White syndrome). Verapamil may also be used in the management of mild to moderate hypertension and renal hypertension.

4.2. Posology and method of administration

For oral administration.

Angina Pectoris

Adults: The usual dosage is 120 mg three times daily.
80 mg three times daily may be satisfactory in some patients with angina of effort. Less than 120 mg three times daily is not likely to be effective in angina at rest and variant angina.

Children: No data are available.

Supraventricular tachycardia

Adults: 40 - 120 mg three times daily according to the severity of the condition.

Children: Up to 2 years: Half a 40 mg tablet 2 to 3 times a day.
2 years and above: One to three 40 mg tablets two to three times daily according to age and effectiveness.

Hypertension

Adults: The usual dosage is 160 mg twice a day. However, a minority of patients may be successfully controlled on 120 mg twice a day while others may require up to 480 mg daily given in divided doses.

Children: Up to 10 mg/kg/day, in divided doses, according to the severity of the disease.

Elderly: The adult dose is recommended unless renal or hepatic function is impaired (see Section 4.4).

Elderly patients show enhanced bioavailability of verapamil and therapeutic control may be achieved with lower doses in this patient population.

Hepatic impairment: Verapamil is extensively metabolised in the 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.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Cardiogenic shock.
- Acute myocardial infarction with complications such as bradycardia.
- Marked hypotension or left ventricular failure.
- Porphyria.
- Hypotension of less than 90 mmHg systolic.
- Bradycardia (< 50 beats / min).
- Uncompensated heart 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).
- Concomitant ingestion of grapefruit juice.
- Patients with atrial flutter/fibrillation in the presence of an accessory pathway (e.g. Wolff-Parkinson-White (WPW) syndrome, Lown-Ganong-Levine syndrome) may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.
- Intravenous dantrolene (see section 4.5).
- 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, as plasma levels of verapamil may be increased (see section 4.2). 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.

Verapamil may affect impulse conduction and should be used with caution in patients with bradycardia or first degree atrioventricular block. The effects of verapamil and beta blockers or other drugs with a cardio-depressive action may be additive both with respect to conduction and contraction, therefore care must be exercised when these are administered concurrently or closely together. This is especially true when either drug is administered intravenously.

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

If there are signs of tachycardia-induced heart failure (energetic exhaustion of the myocardium) digitalisation is necessary before intravenous administration of verapamil.

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.

Special care should be taken in hypotension (see section 4.3), especially in acute myocardial infarction as this is a condition where atrioventricular conduction defects may develop and contractility may be impaired.

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 (see section 4.5 Interaction with other medicinal products and other forms of interaction).

There have been reports of calcium-channel blockers exacerbating muscle weakness in patients with myasthenia gravis. Verapamil should be used with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

Excipient(s)

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

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 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:

Concomitant use contra-indicated

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).With verapamil taken with either disopyramide or flecainide there is an increased risk of myocardial depression and asystole.

Anticoagulants
Verapamil may increase Cmax up to 180% and area under curve (up to 150%) of dabigatran. The risk of bleeding may increase. The dose of dabigatran with oral verapamil may need to be reduced (See dabigatran label for dosing instructions).

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. When verapamil 120 mg immediate -release was co-administered one hour before a single dose of dabigatran etexilate, the dabigatran Cmax was increased by about 180 % and AUC by about 150 %. No meaningful interaction was observed when verapamil was administered 2 hours after dabigatran etexilate (increase of Cmax by about 10% and AUC by about 20%).
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.

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)*.

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. *Ketoconozole*, *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.

A period between stopping beta-blocking therapy and starting therapy with this product may be advisable. Concomitant use of verapamil and beta-blockers or antiarrhythmics, if necessary, should only be administered to patients in a closely monitored clinical setting.

The effects of verapamil may be additive to other hypotensive agents.

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).

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

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 s*imvastatin* 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. Lithium can enhance neuromuscular block during anaesthesia and hence verapamil with lithium may potentiate the neuromuscular blocking effect.

Muscle relaxants
Dantrolene: the association of this muscle relaxant given intravenously and verapamil is potentially dangerous (can cause fatal ventricular fibrillation in animals) and is contraindicated.
Verapamil taken with intravenous dantrolene may cause hypotension, myocardial depression and hyperkalaemia.

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.

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
Animal studies have shown no teratogenic effects and data on a limited number of exposed pregnancies showed no adverse effects on the health of the foetus or newborn child.

Caution should be exercised, however, when prescribing to pregnant women and verapamil should be avoided in the first trimester unless the benefits clearly outweigh the risks. However, verapamil can cause uterine muscle relaxation and this possibility should be considered at term.

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

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 breast-feeding.

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 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 effect 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, paraesthesia, 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 characterised 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.

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

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.

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. Verapamil hydrochloride cannot be removed by haemodialysis.

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 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. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: CO8D A01 Phenylalkylamine derivatives, Calcium channel blockers

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

Absorption
More than 90% of an orally-administered dose of verapamil is absorbed. Due to an intensive hepatic first-pass metabolism, the absolute bioavailability is about 22% with a variability of about 10 - 35%. Under multiple dosing, bioavailability increases by about 30%.

Bioavailability is not affected by food consumption.

Distribution, biotransformation and elimination
Plasma concentrations reach their peak 4 - 8 hours after drug intake. Plasma protein binding of verapamil is about 90%. The elimination half-life is about 5 – 8 hours. The mean residence time of modified-release verapamil is 13 hours. After repeated single daily doses, steady-state conditions are reached between 3 - 4 days.

Within 5 days, approximately 70% of an orally-administered dose is excreted in the urine and about 16% with the faeces. Only 3 - 4 % is eliminated renally as unchanged drug. The drug is extensively metabolized. A number of metabolites are generated in humans (twelve have been identified). Of these metabolites only norverapamil has any appreciable pharmacological effect (approximately 20% that of the parent compound, which was observed in a study with dogs). Norverapamil represents about 6% of the dose eliminated in urine. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. Renal insufficiency does not affect the kinetics of verapamil.

At-risk patients
In patients with liver cirrhosis, bioavailability is increased and elimination half-life is prolonged. In patients with compensated hepatic insufficiency, no influence on the kinetics of verapamil was observed.

5.3. Preclinical safety data

Preclinical information has not been included because the safety profile of verapamil has been established after many years of clinical use. Please refer to section 4.

There is no evidence of teratogenicity or carcinogenicity with verapamil. There are no additional preclinical safety data of relevance to the prescriber.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The tablet contains:
Lactose Monohydrate
Maize Starch
Microcrystalline Cellulose (E460)
Sodium Starch Glycolate (Type A) (E576)
Povidone (E1201)
Silica Colloidal Anhydrous
Magnesium Stearate (E572)
Water, purified

The coating contains:
Hypromellose (E464)
Polyethylene glycol 400 and 4000
Quinolone yellow (E104)
Titanium dioxide (E171)
Iron oxide (E172)
Carnauba Wax: Powder
Water, purified

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

48 months.

6.4. Special precautions for storage

Store at or below 25°C.

6.5. Nature and contents of container

Polypropylene or HDPE containers with polyethylene or LDPE lids or child resistant caps in packs of 100 and 250 tablets.

PVdC coated PVC film with hard temper aluminium foil blister strips in packs of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168 tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point, Whistler Drive
Castleford, WF10 5HX, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 0289/0282

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 November 1993
Date of latest renewal: 25 May 2005

10. DATE OF REVISION OF THE TEXT

15/01/2021