SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Verapamil 120mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains verapamil hydrochloride 120 mg

Excipients with known effect
Lactose
Sunset yellow E110

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Pale yellow, convex, film-coated tablets, diameter approximately 9.5 mm, engraved MP70 on one side.

4.1 Therapeutic indications

1. The management of mild to moderate hypertension and renal hypertension, used alone or in combination with other anti-hypertensive therapy (see section 4.3 for warning regarding concomitant administration with beta-blockers).
2. For the management and prophylaxis of angina pectoris (including variant angina).
3. The treatment and prophylaxis of paroxysmal supraventricular tachycardia and the reduction of the ventricular rate in atrial fibrillation/flutter. Verapamil should not be used for atrial fibrillation / flutter in patients with the Wolff-ParkinsonWhite Syndrome (see section 4.4).

4.2 Posology and method of administration

Posology:

Adults:
Hypertension: 240mg verapamil daily. For patients new to verapamil therapy, the physician should consider halving the initial dose to 120mg. Most patients respond to 240mg daily given as a single dose. If control is not achieved after a

period of at least one week, the dosage may be increased to a maximum of 480mg (in divided doses of 240mg in the morning and 240mg in the evening, at an interval of about twelve hours). A further reduction in blood pressure may be acheived by combining verapamil with other antihypertensive agents, in particular diuretics. 120mg may be used for dose titration purposes.

Angina pectoris: 120 mg twicw daily. A small number of patients respond to a lower dose and where indictaed, adjustment down to 120mg daily could be made. 120mg may be used for dose titration purposes.

Supraventricular paroxysmal tachycardia: 40-120 mg three times a daily depending on the severity of the condition.

Elderly:
The adults dose is recommended unless renal and hepatic function is impaired (see section 4.4, Special Warnings and Precautions for Use).

Children:
Up to 2 years: 20 mg 2-3 times daily.
2 years and above: 40-120 mg 2-3 times daily.

Liver impairment
In patients with impaired liver function, metabolism of the drug is delayed to a greater or lesser extent depending on the severity of hepatic dysfunction, thus potentiating and prolonging the effects of verapamil hydrochloride. Therefore the dosage needs to be adjusted with special caution in patients with impaired liver function and low doses should be given initially (see Special Warnings and Precautions for Use).

Method of administration:

For oral use only
Verapamil tablets should be taken without sucking or chewing, with sufficient liquid, preferably with or shortly after meals

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 block; sino-atrial block; sick sinus syndrome (except in patients with a functioning artificial pacemaker); uncompensated heart failure; marked bradycardia (less than 50 beats/minute). Hypotension (of less than 90 mmHg systolic)
- Patients with atrial flutter/fibrillation in the presence of an accessory pathway (e.g. Wolff-Parkinson-White syndrome) may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.

- Combination with ivabradine (see section 4.5).

4.4 Special warnings and precautions for use

Since verapamil is extensively metabolised in the liver, careful dose titration is required in patients with liver disease. Although the pharmacokinetics of verapamil in patients with renal impairment are not affected, caution should be exercised and careful patient monitoring is recommended. Verapamil is not removed during dialysis.

Heart Block/ 1st Degree AV block/Bradycardia/Asystole

Verapamil hydrochloride affects the AV and SA nodes and prolongs AV conduction time. Use with caution as development of second-or third-degree AV block (contraindication) or unifascicular, bifascicular or trifascicular bundle branch block requires discontinuation in subsequent doses of verapamil hydrochloride and institution of appropriate therapy, if needed.

Verapamil hydrochloride affects the AV and SA nodes and rarely may produce second- or third-degree AV block, bradycardia, and, in extreme cases, asystole. This is more likely to occur in patients with a sick sinus syndrome (SA nodal disease), which is more common in older patients.

Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately (see section 4.8).

Verapamil may affect impulse conduction and should therefore be used with caution in patients with bradycardia or first degree atrioventricular block. 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.

Hypotension

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

Caution should be exercised in treatment with HMG CoA reductase inhibitors (e.g., simvastatin, atorvastatin or lovastatin) for patients taking verapamil. These patients should be started at the lowest possible dose of verapamil and titrated upwards. If verapamil treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g., simvastatin, atorvastatin or lovastatin), refer to advice in the respective statin product

information. Use with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

Verapamil contains lactose and sunset yellow
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose/galactose malabsorption should not take this medicine.

Sunset yellow (E110) may cause allergic reactions.

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 Pglycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of verapamil hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil hydrochloride, therefore, patients should be monitored for drug interactions. Coadministration of verapamil and a drug primarily metabolized by CYP3A4 or being a P-gp substrate may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.
The following are potential drug interactions 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. Phenytoin may decrease the plasma concentrations of verapamil.

Antidepressants
Verapamil may increase the plasma concentrations of imipramine.

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

Antihypertensives, diuretics, vasodilators
Potentiation of the hypotensive effect.

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

Antineoplastics
Verapamil may increase the plasma concentrations of doxorubicin.

Barbiturates
Phenobarbital may reduce the plasma concentrations of verapamil.

Benzodiazepines and other anxiolytics
Verapamil may increase the plasma concentrations of buspirone and midazolam.

Beta blockers
Verapamil may increase the plasma concentrations of metoprolol and propranolol which may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).
Intravenous beta-blockers should not be given to patients 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, 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.

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. Concentration determinations and dose adjustments of everolimus and sirolimus may be necessary.

Inhaled anaesthetics
When used concomitantly, inhalation anaesthetics and calcium antagonists, such as verapamil hydrochloride, should each be titrated carefully to avoid additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Lipid lowering agents
Verapamil may increase the plasma concentrations 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 metabolised 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. Patients receiving both drugs should be monitored carefully.

Neuromuscular blocking agents employed in anaesthesia
The effects may be potentiated.

Serotonin receptor agonists
Verapamil may increase the plasma concentrations of almotriptan.

Theophylline
Verapamil may increase the plasma concentrations of theophylline.

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

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

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

Other
St. John’s Wort may reduce the plasma concentrations of verapamil, whereas grapefruit juice may increase the plasma concentrations of verapamil.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled study data in pregnant women. Although animal studies have not shown any teratogenic effects (see section 5.3), 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.

Verapamil hydrochloride is excreted in human breast milk. Limited human data from oral administration has shown that the infant relative dose of verapamil is low (0.1 – 1% of the mother's oral dose) and that verapamil use may be compatible with breast-feeding. Due to the potential for serious adverse reactions in nursing infants, verapamil should only be used during lactation if it is essential for the welfare of the mother.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Reactions from 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, pruritis, urticaria) are very rarely seen.

Nervous system disorders: headache occur rarely, dizziness, paraesthesia, tremor and extrapyramidal syndrome (e.g. parkinsonism), dystonia.

Ear and labyrinth disorders: vertigo and tinnitus.

Cardiac 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.

Vascular disorders: flushing, peripheral oedema.

Gastrointestinal disorders: nausea and vomiting, constipation is not uncommon, ileus and abdominal pain/discomfort. Gingival hyperplasia may occur very rarely when the drug is administered over prolonged periods. This is fully reversible when the drug is discontinued.

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

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

Reproductive system and breast disorders: impotence (erectile dysfunction) has been rarely reported and isolated cases of galactorrhoea. Gynaecomastia may occur in older male patients under long-term verapamil treatment, which was fully reversible in all cases when the drug was discontinued.

General disorders and administration site conditions: fatigue.

Investigations: On very rare occasions, a reversible impairment of liver function characterised by an increase of transaminase and/or alkaline phosphatase may occur 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 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, 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, acute respiratory distress syndrome 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. In intoxications with large amounts of slow-release preparations (Verapamil), it should be noted that the release of the active drug and the absorption in the intestine may take more than 48 hours. Verapamil hydrochloride cannot be removed by haemodialysis. Depending on the time of ingestion, it should be taken into account that there may be some lumps of incompletely dissolved tablets along the entire length of the gastrointestinal tract, which function as active drug depots.

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

Specific measures to be taken: Elimination of cardiodepressive effects, hypotension or bradycardia. The specific antidote is calcium, e.g. 10-20 ml of a 10% solution of calcium gluconate solution administered intraveneously (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 second or third degree AV block, sinus bradycardia, asystole - atropine, isoprenaline, orcipenaline or pacemaker therapy. In case of hypotension - dopamine, dobutamine, noradrenaline (norepinephrine). If there are signs of continuing myocardial failure - dopamine, dobutamine, if necessary repeated calcium injections.

5.1. Pharmacodynamic properties

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

ATC-Code: C08DA01

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 re-infarction 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 steadystate 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 small intestine after oral administration. Mean systemic availability of the unchanged compound after a single dose of 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 oral administration. The peak plasma concentration of norverapamil is attained approximately five hours after verapamil administration. The presence of food has no effect on the bioavailability of verapamil.

Distribution

Verapamil is widely distributed throughout the body tissues, the volume of distribution ranging from 1.8-6.8 L/kg in healthy subjects. Plasma protein binding of Verapamil is approximately 90%.

Biotransformation

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

Elimination

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

Special Populations

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 haemodialysis.

Hepatic insufficiency:

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

5.3 Preclinical safety data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 0.6 (180 mg/m^2/day) and 1.2 times (360 mg/m^2/day) respectively the equivalent maximum recommended human oral daily dose (300 mg/m^2/day) and have revealed no evidence of teratogenicity. In the rat the highest dose was embryocidal and retarded foetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and reduced weight gain of dams). This oral dose has also been shown to cause hypotension in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Maize Starch
Lactose monohydrate
Gelatin
Silica, colloidal anhydrous
Talc
Magnesium stearate

Tablet coat:
Titanium dioxide
Hydroxypropyl cellulose
Quinoline yellow E104
Sunset yellow E110
Hydroxypropyl methylcellulose 2910
Ethylcellulose
Diethyl phthalate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Container: 2 years
Blister pack: 3 years

6.4 Special precautions for storage

Containers: Do not store above 25ºC. Keep the container tightly closed.

Blister Packs: Do not store above 25ºC. Store in the original package to protect from light.

6.5 Nature and contents of container

Tablets containers: High density polystyrene with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane or polythene inserts.

Blister packs: 250 micron PVC and 25 micron aluminium foil coated with heat resistant print primer on one side and heat-seal lacquer on the other.

Containers of 100 and 500 tablets.
Blister packs of 28 and 84 tablets.

6.6 Special precautions for disposal

The tablets should not be chewed or sucked.

Any unused product or waste material should be disposed of in accordance with

local requirements.

7 MARKETING AUTHORISATION HOLDER

Genethics Europe Limited
41 - 43 Klimentos
Klimentos Tower
Nicosia 1061
Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 42976/0040

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10 DATE OF REVISION OF THE TEXT

14/04/2026