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For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

VASOPTEN

(Verapamil Tablets BP 40 mg, 80mg and 120 mg)

COMPOSITION

CLINICAL PARTICULARS

Therapeutic indications

Vasopten is the drug of choice in treating cases of paroxysmal superaventricular tachycardia, in both the type of angina (vasospastic as well as chronic stable angina) and also in the management of hypertension.

Posology and method of administration

Adults:

Hypertension: initially 120mg twice daily increasing to 160mg twice daily where necessary. In some cases doses of up to 480mg daily, in divided doses, have been used. A further reduction in blood pressure may be obtained by combining verapamil with other antihypertensive agents, in particular diuretics. For concomitant administration with beta-blockers, see section special warnings and precautions for use.

Angina: 120mg three times daily is recommended. 80mg three times daily may be completely satisfactory in some patients with angina of effort. Less than 120mg three times daily is unlikely to be effective in variant angina.

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

Children:

A paradoxical increase in the rate of arrhythmias in children has been noted. Therefore, verapamil should only be used under expert supervision.

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

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

Elderly: The adult dose is recommended unless liver or renal function is impaired.

Method of Administration

For oral administration.

CONTRAINDICATIONS

- Hypersensitivity to verapamil or to any of the excipients.
- Hypotension (of less than 90mmHg systolic)
- Second or third degree atrioventricular block; sick sinus syndrome (except in patients with a functioning artifical pacemaker); uncompensated heart failure; marked bradycardia (less than 50 beats/minute).
- Combination with beta-blockers is contraindicated in patients with poor ventricular function.
- Wolff-Parkinson-White syndrome.
- Concomitant ingestion of grapefruit juice is contraindicated.
- Acute myocardial infarction complicated by bradycardia, marked hypotension or left ventricular failure.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Verapamil may affect left ventricular contractility as a result of its mode of action. The effect is small and not normally important. However, cardiac failure may be aggravated or precipitated if it exists. In cases with poor ventricular function, verapamil should therefore only be administered after appropriate therapy for cardiac failure such as digitalis, etc.

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

Caution should be observed in the acute stage of myocardial infarction.

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

Since verapamil is extensively metabolised in the liver, careful dose titration of verapamil is required in patients with liver disease. The disposition of verapamil in patients with renal impairment has not been fully established and therefore careful patient monitoring is recommended. Verapamil is not removed during dialysis.

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.

H_2 Receptor antagonists

Cimetidine increases serum levels of verapamil.

Anticonvulsants:

Increased serum levels of carbamazepine which could lead to increased side-effects.

Reduced serum levels of verapamil when taken with phenytoin.

Barbiturates:

Reduced serum levels of verapamil when taken with Phenobarbital.

Lithium:

Serum levels of lithium may be reduced (pharmacokinetic effect). There may be increased sensitivity to lithium causing enhanced neurotoxicity (pharmacodynamic effect).

Alcohol:

Verapamil has been shown to increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

Antihypertensive drugs:

Verapamil may have an additive effect with other antihypertensive drugs; thus, in many cases with verapamil, a reduction in the dosage of the other antihypertensive drug may be possible:

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.

Alpha blockers:

Verapamil may increase the plasma concentrations of prazosin and terazosin which may have an additive hypotensive effect.

Antiarrhythmics:

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).

Benzodiazepines and anxiolytics:

Verapamil may increase the plasma concentrations of midazolam.

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.

Acetylsalicylic acid

Concomitant use of verapamil with aspirin may increase the risk of bleeding.

Anti-infectives

Reduced serum levels of verapamil when taken with rifampicin.

Erythromycin, clarithromycin and telithromycin may increase the plasma concentrations of verapamil.

Anaesthesia:

Long-term verapamil therapy may give rise to potentiation of neuromuscular blocking agents during anaesthesia.

Interactions have been reported during the concomitant use of verapamil and the following medications:

Theophylline:

Increased serum levels of theophylline which could lead to increased side-effects.

Immunosuppressants

Verapamil may increase the plasma concentrations of ciclosporin, everolimus, sirolimus and tacrolimus which could lead to increased side-effects.

Digoxin:

Verapamil has been shown to increase the serum concentration of digoxin and caution should therefore be exercised with regard to digitalis toxicity.

Dantrolene

Concomitant use of verapamil with intravenous dantrolene may cause hypotension, myocardial depression, and hyperkalaemia. This combination should be avoided.

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.

Other:

An increase in verapamil serum level has been reported when taken with grapefruit juice.

PREGNANCY AND LACTATION

Animal studies have shown no teratogenic effect. Verapamil should not be administered during pregnancy unless, in the clinicians judgement, it is essential for the welfare of the patient. The possibility that verapamil can reduce uterine blood flow and and cause relaxation of the uterine muscle with fetal hypoxia should be considered at term. Avoid in first trimester unless absolutely necessary, may inhibit labour

Verapamil is excreted in breast milk at concentrations approximately equal to 0.5-1.0 times that coexisting in maternal plasma. However, the amount ingested in such circumstances is less than 1% of the recommended therapeutic infant dose, assuming normal suckling rates.

Effects on ability to drive and use machines

Depending on individual susceptibility, the patient's ability to drive or operate machines may be impaired due to feelings of drowsiness. This is particularly true in the initial stages of treatment, or when changing over from another drug. Verapamil has been shown to increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

UNDESIRABLE EFFECTS

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

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

Ear and labyrinth disorders: vertigo, tinnitus.

Cardiac disorders: bradycardic arrhythmias such as sinus bradycardia, sinus arrest with asystole, 2nd and 3rd degree AV block, bradyarrhythmia in atrial fibrillation, palpitations, tachycardia, development or aggravation of heart failure, hypotension.

Vascular disorders: flushing, peripheral oedema.

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

Skin and subcutaneous tissue disorders: alopecia, ankle oedema, Quincke's oedema, Steven-Johnson syndrome, erythema multiforme, erythromelalgia, 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. Gynaecomastia was observed on very rare occasions in elderly male patients under longer 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 in transaminases and/or alkaline phosphatase, may occur during verapamil treatment and is most probably a hypersensitivity reaction.

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

The following measures may also be necessary: In case of 2nd or 3rd degree AV block, sinus bradycardia, asystole - atropine, isoprenaline, orciprenaline 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Verapamil hydrochloride is a calcium channel blocker and is classified as a class IV anti-arrhythmic agent.

Verapamil inhibits the entry of calcium into smooth muscle cells of the systemic and coronary arteries and in the cells of cardiac muscle and the intracardiac conduction system.

Verapamil lowers peripheral vascular resistance with little or no reflex tachycardia. Its efficacy in reducing both raised systolic and diastolic blood pressure is thought to be primarily due to this mode of action.

The decrease in systemic and coronary vascular resistance and the sparing effect on intracellular oxygen consumption appear to explain the anti-anginal properties of the product.

Due to the effect on the movement of calcium in the intracardiac conduction system, verapamil reduces automaticity, decreases conduction velocity and increases the refractory period.

Pharmacokinetic properties

Verapamil is approximately 90% absorbed from the gastrointestinal tract, but is subject to very considerable first-pass metabolism in the liver and the bioavailability is only about 20%.

Verapamil exhibits bi- or tri-phasic elimination kinetics and is reported to have a terminal plasma half-life of 2-8 hours following a single oral dose. After repeated oral doses this increases to 4.5-12 hours. Verapamil acts within 1-2 hours after oral administration with a peak plasma concentration after 1-2 hours. There is considerable inter individual variation in plasma concentrations.

Verapamil is about 90% bound to plasma proteins. It is extensively metabolised in the liver to at least 12 metabolites of which norverapamil has been shown to have some activity. About 70% of a dose is excreted by the kidneys in the form of its metabolites but about 16% is also excreted in the bile into the faeces. Less than 4% is excreted unchanged.

Verapamil crosses the placenta and is excreted in breast milk.

Preclinical safety data

Not applicable.

EXPIRY DATE

Three Years from the date of Manufacturing.

PACKAGING INFORMATION

Vasopten is available in strips of 10 tablets containing verapamil hydrochloride 40, 80 or 120 mg.

STORAGE AND HANDLING INSTRUCTIONS

Store below 30°C. Protected from Light.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.