ANGIVERA 40/80
Verapamil Tablets BP 40 mg/80 mg

ANGIVERA 40
COMPOSITION:
Each Film Coated Tablet Contains:
Verapamil Hydrochloride BP 40 mg
Excipients q.s.
Colour: Tartrazine

ANGIVERA 80
COMPOSITION:
Each Film Coated Tablet Contains:
Verapamil Hydrochloride BP 80 mg
Excipients q.s.
Colour : Titanium Dioxide BP

DESCRIPTION:
ANGIVERA (Verapamil Tablets BP 40 mg/80 mg) contains Verapamil as an active.

PHARMACODYNAMICS:
Pharmacodynamic properties
Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives.
ATC code: C08 DA01

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.

Pharmacokinetic Properties
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%.
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).

THERAPEUTIC INDICATIONS:
ANGIVERA (Verapamil Tablets BP 40 mg/80 mg) is indicated in treatment of:
1) The management of mild to moderate hypertension and renal hypertension, used alone or in combination with other antihypertensive therapy
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 Wolff-Parkinson-White syndrome

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Adults:
Hypertension: initially 120 mg twice daily increasing to 160 mg twice daily where necessary. In some cases, doses of up to 480 mg 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.
Angina: 120 mg three times daily is recommended. 80 mg three times daily may be completely satisfactory in some patients with angina of effort. Less than 120 mg three times daily is unlikely to be effective in variant angina.
Supraventricular tachycardias: 40-120 mg three times daily depending on the severity of the condition.
Paediatric population:
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: 20 mg 2-3 times a day.
2 years and above: 40-120 mg 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.

CONTRAINDICATION:
- Hypersensitivity to the active substance or to any of the excipients.
- Hypotension (of less than 90 mm Hg systolic)
- Second or third degree atrioventricular block; sick sinus syndrome (except in patients with a functioning artificial 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.
- Combination with ivabradine.

SPECIAL WARNING AND PRECAUTION 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.
Verapamil may affect impulse conduction and should therefore be used with caution in patients with bradycardia or first degree AV 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.
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).

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.
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.
Immuno suppressants: 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.
Metformin: Co-administration of verapamil with metformin may reduce the efficacy of metformin.
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 (150mg), 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 240mg 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.

PREGNANCY, BREAST-FEEDING AND FERTILITY
There are no adequate and well-controlled study data in pregnant women. Although animal studies have not shown any teratogenic effects, verapamil should not be given during the first trimester of pregnancy unless, in the clinicians 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 breastfeeding. 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.

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, 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.

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.

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, metabolic acidosis and acute respiratory distress syndrome. 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

SHELF LIFE:
36 Months

PACKAGING
10 Tablets are packed in Alu-Alu Blister & such 1 Blister is packed in printed carton along with pack insert.

STORAGE CONDITION:
Stored at a temperature not exceeding 30°C. Protect from light and moisture.
Keep the medicine out of reach of children.

Imported by:
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