# Isoptin® SR 240mg

**Active drug substance: verapamil hydrochloride**

**Film coated tablets with prolonged action**

**Calcium antagonist for the treatment of hypertension**

**QUALITATIVE AND QUANTITATIVE COMPOSITION**
Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). The chemical name of verapamil hydrochloride is benzeneacetonitrile, α-[3-[{2-(3, 4-dimethoxyphenyl) ethyl} methylamino] propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride. It has a molecular weight of 491.07 and the molecular formula is C27H38N204•HCl.

**Composition**
1 film coated tablet contains 240mg of verapamil hydrochloride.

**PHARMACEUTICAL FORM**

Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, freely soluble in chloroform, sparingly soluble in alcohol and practically insoluble in ether.

**CLINICAL PARTICULARS**

**Therapeutic Indications**
Hypertension

**Posology and method of administration**
The doses of Isoptin® SR 240mg, individualized according to the severity of the disease, are to be taken regularly as prescribed by the physician. The film coated tablets are to be swallowed whole with some fluid, preferably with or shortly after meals. Unless otherwise instructed, the daily dose for adults is 1 film coated tablet in the morning (patients requiring particularly gradual blood pressure lowering should be started on half tablet taken in the morning). If after about 2 weeks of treatment a dose increase is found to be necessary the dose can be raised to a maximum of 2 film coated tablets daily (additionally 1 half to 1 film coated tablet in the evening after an interval of about 12 hours). On long-term treatment a daily dose of 480mg should not be exceeded; short-term dose increases are possible only when directed by the physician. For children and adults requiring smaller doses of verapamil, Isoptin® 40mg and 80mg are available. In patients with impaired hepatic function the effect of verapamil is intensified and prolonged depending on the severity of the liver disease due to the diminished drug metabolism. In these cases dosage should be adjusted with special care starting with low doses (eg. in patients with hepatic cirrhosis with 1 tablet 40mg 2-3 times daily).

**Special Population**

**Renal Impairment**
Current available data are described in *Special Warnings and Precautions for Use* Section. Verapamil hydrochloride should be used cautiously and with close monitoring in patients with impaired renal function.

**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* Section).

**Method of administration**
For oral use only.
Tablets should be taken without sucking or chewing, with sufficient liquid, preferably with or shortly after meals.

**Contraindications**
- Hypersensitivity to verapamil hydrochloride or to any of the inactive ingredients
- Cardiogenic shock
- Second or third degree AV block (except in patients with a functioning artificial pacemaker)
- Sick sinus syndrome (except in patients with a functioning artificial pacemaker)
- Congestive heart failure and/or severe left ventricular dysfunction (e.g. reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mmHg), unless secondary to a supraventricular tachycardia amenable to verapamil therapy.
- Atrial fibrillation/flutter in the presence of an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.
- Acute myocardial infarction with complications (bradycardia, marked hypotension, left ventricular failure) and sinoatrial block
- Combination with Ivabradine (See *Interaction with other medicinal products and other forms of interaction* section)

**Special warnings and precautions for use**

**Heart Block/First degree AV block/Asystole/Bradycardia (<50 beats/min)**
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 *Undesirable Effects* section.

**Anti-arrhythmic and Beta blockers**
Mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure and potentiated hypotension). Asymptomatic bradycardia (36 beats/minute) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil hydrochloride.

**Digoxin**
If verapamil is administered concomitantly with digoxin, reduce digoxin dosage. See *Interactions with other medicinal drug products and other forms of interaction* section.

**Heart Failure**
Heart failure patients with ejection fraction higher than 35% should be compensated before starting verapamil treatment and should be adequately treated throughout.

**Hypotension**
Hypotensive symptoms of lethargy and weakness with faintness have been reported following single oral doses and even after some months of treatment. In some patients it may be necessary to reduce the dose of verapamil hydrochloride.

**HMG-CoA Reductase Inhibitors ("Statins")**
See *Interaction with other medicinal products and other forms of interaction* section

**Neuromuscular transmission disorders**
Verapamil hydrochloride 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).

**Ventricular Tachycardia**
The risk of inducing ventricular tachycardia cannot be excluded.

**Other Special Populations**

**Renal impairment**
Although impaired renal function has been shown in robust comparator studies to have no effect on verapamil pharmacokinetics in patients with end-stage renal failure, several case reports suggest that verapamil should be used cautiously and with close monitoring in patients with impaired renal function. Verapamil cannot be removed by hemodialysis.

**Liver impairment**
Use with caution in patients with severely impaired liver function (see also *Posology section on liver impairment*)

**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. Co-administration 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 table provides a list of potential drug interactions due to pharmacokinetic reasons:

| **Potential Interactions** | | |
|---|---|---|
| **Concomitant drug** | **Potential effect on verapamil or concomitant drug** | **Comment** |
| **Alpha blockers** | | |
| Prazosin | ↑ prazosin $C_{max}$ (~40%) with no effect on half-life | Additive hypotensive effect |
| Terazosin | ↑ terazosin AUC (~24%) and $C_{max}$ (~25%) | |
| **Antiarrhythmics** | | |
| Flecainide | Minimal effect on flecainide plasma clearance (<~10%); no effect on verapamil plasma clearance | See *Special warnings and precautions for use* section |
| Quinidine | ↓ oral quinidine clearance (~35%) | Hypotension and/or pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy. |
| **Antiasthmatics** | | |
| Theophylline | ↓ oral and systemic clearance by ~20% | Reduction of clearance was lessened in smokers (~11%) |
| **Anticonvulsants/ Anti-epileptics** | | |
| Carbamazepine | ↑ carbamazepine AUC (~46%) in refractory partial epilepsy patients | Increased carbamazepine levels.<br>This may produce carbamazepine side effects such as diplopia, headache, ataxia or dizziness. |
| Phenytoin | ↓ verapamil plasma concentrations | |
| **Antidepressants** | | |
| Imipramine | ↑ imipramine AUC (~15%) | No effect on level of active metabolite, desipramine |
| **Antidiabetics** | | |
| Glyburide | ↑ glyburide $C_{max}$ (~28%), AUC (~26%) | |
| Metformin | | Co-administration of verapamil with metformin may reduce the efficacy of metformin. |
| **Anti-gout** | | |
| Colchicine | ↑ colchicine AUC (~ 2.0-fold) and Cmax (~1.3-fold) | Combined use of verapamil and colchicine is not recommended |
| **Anti-infectives** | | |
| Clarithromycin | Possible ↑ in verapamil levels | |
| Erythromycin | Possible ↑ in verapamil levels | |

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|---|---|---|
| Rifampicin | ↓ verapamil AUC (~97%), $C_{max}$ (~94%), oral bioavailability (~92%)<br>No change in PK with intravenous verapamil administration | Blood pressure lowering effect may be reduced. |

| | | |
|---|---|---|
| Telithromycin | Possible ↑ in verapamil levels | |
| **Antineoplastics** | | |
| Doxorubicin | ↑ doxorubicin AUC (104%) and $C_{max}$ (61%) with oral verapamil administration | In patients with small cell lung cancer |
| | No significant change in doxorubicin PK with intravenous verapamil administration | In patients with advanced neoplasms |
| **Barbiturates** | | |
| Phenobarbital | ↑ oral verapamil clearance (~5-fold) | |
| **Benzodiazepines and other anxiolytics** | | |
| Buspirone | ↑ buspirone AUC, $C_{max}$ by ~3.4-fold | |
| Midazolam | ↑ midazolam AUC (~3-fold) and $C_{max}$ (~2-fold) | |
| **Beta blockers** | | |
| Metoprolol | ↑ metoprolol AUC (~32.5%) and $C_{max}$ (~41%) in angina patients | See *Special warnings and precautions for use* section |
| Propranolol | ↑ propranolol AUC (~65%) and $C_{max}$ (~94%) in angina patients | |
| **Cardiac glycosides** | | |
| Digitoxin | ↓ digitoxin total body clearance (~27%) and extrarenal clearance (~29%) | |
| Digoxin | Healthy subjects: ↑ digoxin $C_{max}$ by ~44%, ↑ digoxin $C_{12h}$ (~53%), ↑ digoxin $C_{ss}$ by ~44% and ↑ digoxin AUC by ~50% | Reduce digoxin dosage. Also see *Special warnings and precautions for use* section |
| **$H_2$ receptor antagonists** | | |
| Cimetidine | ↑ AUC of R- (~25%) and S- (~40%) verapamil with corresponding ↓ in R- and S-verapamil clearance | Cimetidine reduces verapamil clearance following intravenous verapamil administration |
| **Immunologics/ Immuno-suppressives** | | |
| Cyclosporine | ↑ cyclosporine AUC, $C_{ss}$, $C_{max}$ by ~45% | |
| Everolimus | Everolimus: ↑ AUC (~3.5-fold) and ↑ Cmax (~2.3-fold)<br>Verapamil: ↑ Ctrough (~2.3-fold) | Concentration determinations and dose adjustments of everolimus may be necessary |
| Sirolimus | Sirolimus ↑ AUC (~2.2-fold); S-verapamil ↑ AUC (~1.5-fold) | Concentration determinations and dose adjustments of sirolimus may be necessary |
| Tacrolimus | Possible ↑ tacrolimus levels | |
| **Lipid lowering agents (HMG COA reductase inhibitors)** | | |
| Atorvastatin | Possible ↑ atorvastatin levels<br>↑ verapamil AUC by ~43% | Additional information follows |
| Lovastatin | Possible ↑ lovastatin levels<br>↑ verapamil AUC (~63%) and $C_{max}$ (~32%) | |
| Simvastatin | ↑ simvastatin AUC (~2.6-fold), $C_{max}$ (~4.6-fold) | |
| **Serotonin receptor agonists** | | |
| Almotriptan | ↑ almotriptan AUC (~20%), ↑ $C_{max}$ (~24%) | |
| **Uricosurics** | | |
| Sulfinpyrazone | ↑ verapamil oral clearance (~3-fold)<br>↓ bioavailability (~60%) | Blood pressure lowering effect may be reduced |
| | No change in PK with intravenous verapamil administration | |
| **Anticoagulants** | | |
| Dabigatran | <u>Verapamil immediate release</u><br>↑ dabigatran (Cmax up to 180%) and AUC (up to 150%)<br><u>Verapamil sustained release</u><br>↑ dabigatran (Cmax up to 90%) and AUC (up to 70%) | The risk of bleeding may increase. The dose of dabigatran with oral verapamil may need to be reduced. (See dabigatran label for dosing instructions). |
| 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 oral verapamil may need to be reduced (see DOAC label or dosing instructions). |
| **Other Cardiac therapy** | | |
| Ivabradine | Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of verapamil to ivabradine | See *Contraindications* section |
| **Other** | | |

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|---|---|---|
| Grapefruit juice | ↑ R- (~49%) and S- (~37%) verapamil AUC<br>↑ R- (~75%) and S- (~51%) verapamil $C_{max}$ | Elimination half life and renal clearance not affected. Grapefruit juice should therefore not be ingested with verapamil. |
| St. John's W ort | ↓ R- (~78%) and S- (~80%) verapamil AUC with corresponding reductions in $C_{max}$ | |

**Other Drug Interactions and Additional Drug Interaction Information**

***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.

***Lithium***
Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil hydrochloride-lithium therapy with either no change or an increase in serum lithium levels. The addition of verapamil hydrochloride, however, has also resulted in the lowering of the serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs should be monitored carefully.

***Neuromuscular blockers***
Clinical data and animal studies suggest that verapamil hydrochloride may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil hydrochloride and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly

***Acetylsalicylic acid***
Increased tendency to bleed

***Ethanol (alcohol)***
Elevation of ethanol plasma levels

***HMG Co-A Reductase Inhibitors ("Statins")***
Treatment with HMG CoA reductase inhibitors (eg. 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. Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.

***Antihypertensives, diuretics, vasodilators***
Potentiation of the hypotensive effect

**Pregnancy and lactation**

**Pregnancy**
There are no adequate and well-controlled study data in pregnant women. Verapamil crosses the placenta and has been measured in umbilical cord blood. Verapamil hydrochloride should not be given during pregnancy (especially in the first trimester) unless, in the physician's judgement, it is essential for the patient's well-being (see *Preclinical Safety Data* Section).

**Lactation**
Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. Verapamil hydrochloride/metabolites are excreted in human 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). A risk to the newborns/infants cannot be excluded. 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**
Due to its hypotensive effect, depending on the individual response, verapamil hydrochloride may affect the ability to react to the point of impairi ng the ability to drive a vehicle, operate machinery or work under hazardous conditions. This applies all the more at the start of treatment when the dose is raised, when switching from another drug and in conjunction with alcohol. Verapamil may increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

**Undesirable effects**
The following adverse events reactions have been reported with verapamil from clinical studies, postmarketing surveillance or Phase IV clinical trials and are listed below by system organ class. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

The most commonly reported adverse drug reactions were headache, dizziness, gastrointestinal disorders: nausea, constipation and abdominal pain, as well as bradycardia, tachycardia, palpitations, hypotension, flushing, edema peripheral and fatigue.

**Adverse reactions reported from clinical studies with verapamil and post-marketing surveillance activities**

| MedDRA System Organ Class | Common | Uncommon | Rare | Unknown |
|---|---|---|---|---|
| **Immune** system disorders | | | | Hypersensitivity |
| **Nervous** system disorders | Dizziness,<br>Headache | | Paresthesia<br>Tremor | Extrapyramidal disorder, paralysis (tetraparesis)[1]<br>Seizures |
| **Metabolism** and nutrition disorders | | | | Hyperkalaemia |
| **Psychiatric** disorders | | | Somnolence | |
| **Ear** and labyrinth disorders | | | Tinnitus | Vertigo |
| **Cardiac** disorders | Bradycardia | Palpitations,<br>Tachycardia | | Atrioventricular block (1°, 2°, 3°), Cardiac failure, Sinus arrest, Sinus bradycardia; asystole |
| **Vascular** disorders | Flushing,<br>Hypotension | | | |
| **Respiratory**, thoracic and mediastinal disorders | | | | Bronchospasm, Dyspnoea |
| **Gastrointestinal** disorders | Constipation,<br>Nausea | Abdominal pain | Vomiting | Abdominal discomfort, Gingival hyperplasia, Ileus |

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|---|---|---|---|---|
| **Skin** and subcutaneous tissue disorders | | | Hyperhidrosis | Angioedema, Stevens-Johnson syndrome, Erythema multiforme, Alopecia, Itching, Pruritus, Purpura, Rash maculopapular, Urticaria |
| **Musculoskeletal** and connective tissue disorders | | | | Arthralgia, Muscular weakness, Myalgia |
| **Renal** and urinary disorders | | | | Renal failure |
| **Reproductive system and breast disorders** | | | | Erectile dysfunction, Galactorrhea, Gynecomastia |
| **General disorders** and administration site conditions | Edema peripheral | Fatigue | | |
| **Investigations** | | | | Blood prolactin increased, Hepatic enzymes increased |

[1]There has been a single postmarketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended. See *Interactions with other medicinal products and other forms of interaction* section.

**Reporting of suspected adverse reactions**
Reporting of suspected adverse reactions is an important way to gather more information to continuously monitor the benefit/risk balance of the medicinal product.

**Overdosage**

**Clinical Manifestations**
Hypotension, bradycardia up to high degree AV block and sinus arrest, hyperglycemia, stupor, metabolic acidosis and acute respiratory distress syndrome. Fatalities have occurred as a result of overdose.

**Treatment**
Treatment of verapamil hydrochloride overdose should be mainly supportive and individualized. Beta adrenergic stimulation and/or parenteral administration of calcium injection (calcium chloride) have been effectively used in treatment of deliberate overdosage with oral verapamil hydrochloride. Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including beta adrenergic stimulation (e.g., isoproterenol hydrochloride), other vasopressor agents or cardiopulmonary resuscitation. Due to the potential for delayed absorption of the sustained release product, patients may require observation and hospitalization for up to 48 hours. Verapamil hydrochloride cannot be removed by hemodialysis.

**PHARMACOLOGICAL**

**PROPERTIES**

**Pharmacodynamic properties**
Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine

derivatives. ATC-Code: C08DA01

Verapamil hydrochloride is a white or practically white crystalline powder. It is practically odorless and has a bitter taste. It is soluble in water, freely soluble in chloroform, sparingly soluble in alcohol and practically insoluble in ether. The chemical name of verapamil hydrochloride is benzeneacetonitrile, α-[3-[{2- (3,4-dimethoxyphenyl)ethyl}methylamino] propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride. It has a molecular weight of 491.07 and the molecular formula is C27H38N204 • HCl.

Mechanism of action and Pharmacodynamic effects
Verapamil inhibits the calcium ion (and possibly sodium ion) influx through slow channels into conductile and contractile myocardial cells and vascular smooth muscle cells. The antiarrhythmic effect of verapamil appears to be due to its effect on the slow channel in cells of the cardiac conductile system. Electrical activity through the sinoatrial (SA) and atrioventricular (AV) nodes depends, to a significant degree, upon calcium influx through the slow channel. By inhibiting this influx, verapamil slows AV conduction and prolongs the effective refractory period within the AV node in a rate-related manner. This effect results in a reduction of the ventricular rate in patients with atrial flutter and/or atrial fibrillation and a rapid ventricular response. By interrupting reentry at
the AV node, verapamil can restore normal sinus rhythm in patients with paroxysmal supraventricular tachycardias (PSVT), including W olff-Parkinson White (W -P-W ) syndrome. Verapamil has no effect on conduction across accessory bypass tracts.

Clinical efficacy and safety
Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibers. In the isolated rabbit heart, concentrations of verapamil that markedly affect SA nodal fibers or fibers in the upper and middle regions of the AV node have very little effect on fibers in the lower AV node (NH region) and no effect on atrial action potentials or His bundle fibers. Verapamil does not induce peripheral arterial spasm nor does it alter total serum calcium levels. Verapamil reduces afterload and myocardial contractility.
In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index is usually not reduced, but in patients with moderately severe to severe cardiac dysfunction (pulmonary wedge pressure above 20 mm Hg, ejection fraction less than 30%), acute worsening of heart failure may be seen. Peak therapeutic effects occur within three to five minutes after a bolus injection of verapamil. The commonly used intravenous doses of 5 to 10 mg verapamil hydrochloride produce transient, usually asymptomatic, reduction in normal systemic arterial pressure, systemic vascular resistance and contractility; left ventricular filling pressure is slightly increased.

**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 IR verapamil is 22% and that of SR verapamil 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 feces. 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**
*Pediatric*: Limited information on the pharmacokinetics in the paediatric population is available. Steady-state plasma concentrations appear to be somewhat lower in the pediatric population after oral dosing compared to those observed in adults.

*Geriatric*: 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.

**Preclinical safety data**
Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are, however, no adequate and well-controlled studies in pregnant women.

**PHARMACEUTICAL PARTICULARS List of excipients**
Cellulose, Montan Glycol Wax, Macrogols (Type 400 and Type 6000), Magnesium stearate, Hypromellose, Povidone, Quinoline yellow, Indigo Carmine, Sodium alginate, Talc, Titanium dioxide, Ethanol anhydrous, Purified water

**Shelf Life**
3 years
Do not use beyond the expiry date indicated on the carton.

**Special precautions for storage**
Store the drug carefully at or below 25°C. Keep out of the reach of children.

**Nature and Contents of Container**
PVC/PVDC blister with aluminum foil
15 tablets per blister. 2 blisters per pack.
Manufactured by AbbVie Deutschland GmbH & Co. KG, Knollstrasse, 67061 Ludwigshafen, Germany / FAMAR A.V.E. ANTHOUSSA PLANT, Anthoussa
Avenue 7 Anthoussa Attiki 15349, Greece

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