ISOPTIN®

VERAPAMIL HYDROCHLORIDE

NAME OF THE MEDICINAL PRODUCT

Isoptin® 80 mg, film-coated tablets
Isoptin® SR, 240 mg prolonged-release tablets

COMPOSITION OF THE MEDICINAL PRODUCT

Active substances:

Isoptin 80 mg: One film-coated tablet contains 80 mg of verapamil hydrochloride.

Isoptin SR: One prolonged-release tablet contains 240 mg of verapamil hydrochloride.

DOSAGE FORM

Isoptin 80 mg: Film-coated tablet

Isoptin SR: Prolonged -release tablet

CLINICAL PARTICULARS

Therapeutic indications

- Symptomatic coronary artery disease:
  - chronic stable angina pectoris (exercise-induced angina)unstable angina pectoris (crescendo angina, angina at rest)
  - vasospastic angina pectoris (Prinmetal's angina, variant angina)
  - post-myocardial infarction angina pectoris in patients without heart failure if beta-blockers are not indicated.
- For treatment of cardiac arrhythmia in:
  - paroxysmal supraventricular tachycardia
  - atrial fibrillation/atrial flutter with rapid atrioventricular conduction (except in Wolff-Parkinson-White syndrome).
- Hypertension.

Posology and method of administration

Verapamil hydrochloride, the active substance in Isoptin, should be dosed individually in accordance with the severity of disease. Long-standing clinical experience shows that the average daily dose in almost all indications is between 240 mg and 360 mg. A daily dosage of 480 mg should not be exceeded in long-term therapy; short-term increases are possible.

Unless otherwise prescribed, the following dosage guidelines apply:

For Isoptin 80 mg:

Adults and adolescents weighing over 50 kg:

Coronary heart disease: The recommended daily dosage is 240 mg – 480 mg verapamil hydrochloride in 3 – 4 doses, as follows: 1 Isoptin 80 mg film-coated tablet 3 to 4 times daily (equivalent to 240 mg – 320 mg verapamil hydrochloride per day). For patients requiring higher dosages (e.g. 360 mg – 480 mg verapamil hydrochloride/day), formulations with a more suitable active drug content should be used.

Hypertension: The recommended daily dosage is 240 mg – 360 mg verapamil hydrochloride in 3 doses, as follows: 1 Isoptin 80 mg film-coated tablet 3 times daily (equivalent to 240 mg verapamil hydrochloride per day). For patients requiring higher doses (e.g. 360 mg verapamil hydrochloride/day), formulations with a more suitable active drug content should be used.

Paroxysmal supraventricular tachycardia, atrial fibrillation/atrial flutter: The recommended daily dosage is 240 mg – 480 mg verapamil hydrochloride in 3 – 4 doses, as follows: 1 Isoptin 80 mg film-coated tablet 3 to 4 times daily (equivalent to 240 mg – 320 mg verapamil hydrochloride per day). For patients requiring higher dosages (e.g. 360 mg - 480 mg verapamil hydrochloride/day), formulations with a more suitable active drug content should be used.

Children (only for heart rate disorders):

Older preschool children up to age 6: The recommended daily dosage is 80 mg – 120 mg verapamil hydrochloride in 2 – 3 doses. Formulations with a suitable active drug content are available (40 mg verapamil hydrochloride).

Schoolchildren aged 6 - 14: The recommended daily dosage is 80 mg - 360 mg verapamil hydrochloride in 2 – 4 doses, as follows: 1 Isoptin 80 mg film-coated tablet 2 to 4 times daily (equivalent to 160 mg – 320 mg verapamil hydrochloride per day). Isoptin 80 mg is used if lower doses (e.g. 80 mg verapamil hydrochloride per day) have not produced a satisfactory response. For patients requiring higher doses (e.g. 360 mg verapamil hydrochloride/day), formulations with a more suitable active drug content should be used.

For Isoptin SR:

Adults and adolescents weighing over 50 kg:

Coronary heart disease: The recommended daily dosage is 240 mg – 480 mg verapamil hydrochloride in 2 doses, as follows: ½ - 1 Isoptin SR 240mg tablet 2 times daily (equivalent to 240 mg – 480 mg verapamil hydrochloride per day). Isoptin SR 240mg tablet is used if lower doses (e.g. 240 mg verapamil hydrochloride per day) have not produced a satisfactory response.

Hypertension: The recommended daily dosage is 240 mg – 480 mg verapamil hydrochloride in 1 – 2 doses, as follows: 1 Isoptin SR 240mg tablet once a day in the morning (equivalent to 240 mg verapamil hydrochloride per day). If the response is unsatisfactory, add ½ - 1 Isoptin SR 240mg tablet in the evening (equivalent to 360 mg - 480 mg verapamil hydrochloride per day).

Paroxysmal supraventricular tachycardia, atrial fibrillation/atrial flutter: The recommended daily dosage is 240 mg – 480 mg verapamil hydrochloride in 2 doses, as follows: ½ - 1 Isoptin SR 240mg tablet 2 times daily (equivalent to 240 mg – 480 mg verapamil hydrochloride per day). Isoptin SR 240mg tablet is used if lower doses (e.g. 240 mg verapamil hydrochloride per day) have not produced a satisfactory response.

Impaired liver function: In patients with impaired liver function, the effect of verapamil hydrochloride is enhanced and prolonged due to slower metabolism of the drug and depending on the degree of impairment. Therefore, the dosage needs to be adjusted with special caution in such cases, and low doses should be given initially (e.g. 40 mg verapamil hydrochloride 2 – 3 times daily in subjects with impaired liver function, equivalent to
80 mg – 120 mg verapamil hydrochloride per day). The tablets are taken whole without being chewed or sucked, and with sufficient liquid (e.g. a glass of water; not grapefruit juice), preferably with or shortly after meals.

Do not take Isoptin while lying down. Verapamil hydrochloride must not be administered to post-myocardial infarction patients with angina pectoris until 7 days after the acute myocardial infarction event. The product may be taken indefinitely. Isoptin should not be discontinued abruptly after long-term use. Tapering off the dosage is recommended.

Contraindications

Isoptin may not be used in the following cases: Hypersensitivity (allergy) to the active substance verapamil hydrochloride or any of the other ingredients of Isoptin, Cardiovascular shock, Acute myocardial infarction with complications (bradycardia, hypotension, left heart failure), Severe conduction disorders (such as 2nd or 3rd degree SA or AV block), Sick sinus syndrome, Manifest heart failure, Atrial fibrillation and/or flutter accompanied by WPW syndrome (increases risk of triggering ventricular tachycardia), Concomitant intravenous beta-blocker treatment must not be performed in patients receiving Isoptin (except in an intensive care setting).

Special Warnings and Special Precautions for Use

Particularly close medical supervision is necessary in the presence of: 1st degree AV block, Hypotension (systolic BP below 90 mmHg), Bradycardia (heart rate below 50 beats per minute), Severely impaired liver function, Diseases affecting neuromuscular transmission (myasthenia gravis, Eaton-Lambert syndrome, advanced Duchenne's muscular dystrophy).

Drug interactions: Verapamil is a substrate and inhibitor of the P450 3A4 cytochrome. If given at the same time as simvastatin, a substance which is metabolised via the P450 3A4 cytochrome, verapamil may increase simvastatin levels in the blood, and may thereby increase the risk of muscular toxicity. The simvastatin dose should therefore be adjusted accordingly (see manufacturer's product information)

Interactions with other medicinal products and other forms of interaction

The following interactions with this medicinal product must be kept in mind:

Antiarrhythmics (e.g. flecainide, disopyramide), beta-blockers (e.g. metoprolol, propranolol), inhaled anaesthetics: Mutual potentiation of cardiovascular effects (high-grade atrioventricular block, major lowering of heart rate, onset of heart failure, increased lowering of the blood pressure). Concomitant intravenous administration of Isoptin must be avoided in patients receiving beta-blockers (except in an intensive care setting).

Antihypertensives, diuretics, vasodilators: Potentiation of the antihypertensive effect.

Digoxin, digitoxin: Elevation of digoxin plasma levels as a result of diminished renal excretion (monitor for symptoms of digoxin/digitoxin overdose and reduce the glycoside dose, if necessary, after having determined digoxin/digitoxin plasma levels as appropriate).

Quinidine: Excessive blood pressure lowering is possible. Pulmonary oedema may occur in subjects with hypertrophic obstructive cardiomyopathy. Elevation of quinidine plasma level.

Carbamazepine: Potentiation of carbamazepine effect. Enhanced neurotoxicity.

Lithium: Diminished lithium efficacy. Increased lithium neurotoxicity.

Muscle relaxants: Verapamil hydrochloride may potentiate the effects of these medicinal products.

Acetylsalicylic acid: Increased bleeding propensity.

Doxorubicin: Concomitant oral use of doxorubicin and verapamil increases the bioavailability and peak plasma levels of doxorubicin in patients with small cell lung cancer.
No significant changes of doxorubicin pharmacokinetics in association with concomitant intravenous administration of verapamil have been observed in patients with advanced cancer.

Ethanol: Delayed ethanol clearance and elevation of ethanol plasma levels, i.e. verapamil enhances the effect of alcohol.

Interactions due to cytochrome P450 isoenzyme 3A4

Verapamil hydrochloride is primarily metabolised by cytochrome P450 isoenzyme 3A4 in the liver and inhibits this enzyme. Furthermore, verapamil inhibits the P-glycoprotein (P-gp). The following interactions must be observed in this regard:

*Other cytochrome P450 isoenzyme 3A4 inhibitors, such as azole fungicides (e.g. clotrimazol or ketoconazol), protease inhibitors (e.g. ritonavir or indinavir), macrolides (e.g. erythromycin, clarithromycin, telithromycin), cimetidine, serotonin receptor antagonists (e.g. almotriptan), antidepressants (e.g. imipramine), antidiabetics (e.g. glibenclamide), benzodiazepines and other anxiolytics (e.g. buspirone): E*levation of verapamil hydrochloride plasma levels and/or plasma levels of these medicinal products owing to (mutual) effects on drug metabolism.

Cytochrome P450 isoenzyme 3A4 inducers, such as, phenytoin, rifampicine, phenobarbital, carbamazepine, uricosuric agents (e.g. sulfinpyrazone), Hypericum (St. John's wort extract): Lowering of verapamil hydrochloride plasma levels and attenuation of the effect of verapamil hydrochloride.

Cytochrome P450 isoenzyme 3A4 substrates, such as antiarrhythmics (e.g. amiodarone or quinidine), CSE inhibitors (e.g. lovastatin or atorvastatin), midazolam, cyclosporin, sirolimus, tacrolimus, theophylline, prazosine, terazosine: Elevation of the plasma levels of these medicinal products.

Colchicine: Colchicine is a substrate of both the cytochrome P450 isoenzyme CYP3A4 and of the efflux transporter P-glycoprotein (P-gp). Verapamil inhibits CYP3A4 and P-gp. Concomitant administration of verapamil and colchicine may produce elevated colchicine plasma levels owing to vera pamil's inhibitory effect on CYP3A4 and/or P-gp. Simultaneous use of verapamil and colchicine is not recommended.

Simvastatin: The risk of myopathy/rhabdomyolysis is increased when higher doses of verapamil and simvastatin are given concomitantly. The simvastatin dose should therefore be adjusted accordingly (see manufacturer's product information).

Fluvastatin, provastatin and rosuvastatin are not metabolised via the cytochrome P450 isoenzyme 3A4. Interaction with verapamil is therefore less likely to occur.

Note: Food and drinks containing grapefruit should be avoided during Isoptin use. Grapefruit can increase verapamil hydrochloride plasma levels.

Pregnancy and Lactation

Pregnancy: Verapamil hydrochloride crosses the placental barrier. Plasma concentrations in umbilical cord blood are 20% - 92% of those in the mother's blood. The database on verapamil

hydrochloride use during pregnancy is insufficient. However, data from a limited number of pregnancies in women receiving oral treatment does not suggest that verapamil hydrochloride is teratogenic. Animal studies have demonstrated reproductive toxicity.
Therefore, verapamil hydrochloride should not be taken during the first and second trimesters of pregnancy. Verapamil hydrochloride may be taken during the third trimester of pregnancy only if strictly necessary and if the benefits exceed the risks to the mother and child.

Lactation: Since active substance is excreted into breast milk (concentration in milk: approximately 23% of that in the maternal plasma) verapamil hydrochloride should not be taken during the lactation period. There is evidence to indicate that verapamil hydrochloride may cause hyperprolactinaemia and galactorrhoea in isolated cases.

Effects on ability to drive and use machines

Treatment with Isoptin requires regular monitoring by a physician. Depending on individual response, judgment and motor skills may be affected to the point of impairing the ability to drive a vehicle, operate machinery, or work under hazardous conditions. This applies particularly at the beginning of treatment, on increasing the dose or when switching to another medication as well as when alcohol is consumed simultaneously.

Undesirable Effects

The side effects given below may occur during Isoptin treatment. The classification of side effects is based on their rate of incidence as listed below:
Very common: ≥10% Common: ≥1% - < 10%
Uncommon: ≥0.1% - < 1% Rare: ≥0.01% - < 0.1%
Very rare: <0.01%, including isolated cases

Undesirable Effects		
Metabolism	Uncommon	Reduction of glucose tolerance.
Psychological	Common	Fatigue, nervousness.
Nervous System	Common	Dizziness or light-headedness, paresthesia, neuropathy and tremor.
	Very rare	Extrapyramidal symptoms (Parkinson's syndrome, choreoathetosis, dystonic syndromes): experience to date indicates that these side effects resolve when Isoptin is discontinued. A single case of paralysis, specifically affecting the arms and legs (tetraparesis), has been reported during concomitant use of verapamil and colchicine (an agent used to treat gout). Simultaneous use of verapamil and colchicine is not recommended.
Cardiovascular system	Common	Development of heart failure or exacerbation of existing heart failure. Excessive lowering of blood pressure and/or postural hypotension, sinus bradycardia, 1st degree AV block, ankle oedema, flushing, reddening of the skin and a sensation of warmth.
	Uncommon	Palpitations, tachycardia, 2nd or 3rd degree AV block.
	Very rare	Sinus arrest with asystole.
Respiratory tract	Uncommon	Bronchospasm.
Ear and vestibular system	Uncommon	Tinnitus.
Gastrointestinal tract	Very common	Nausea, bloating, constipation.
	Uncommon	Vomiting.
	Very rare	Ileus, gingival hyperplasia (gingivitis, bleeding gums): resolves when Isoptin is discontinued.
Liver	Uncommon	Reversible elevation of hepatic enzymes, probably as a manifestation of allergic hepatitis.
Skin and mucosa (allergic reactions)	Common	Allergic reactions, such as erythema, pruritus, urticaria, maculopapular exanthema, erythromelalgia.
	Rare	Purpura.
	Very rare	Angioneurotic oedema, Stevens-Johnson syndrome, photodermatitis.
Musculoskeletal system	Rare	Arthralgia, myalgia, weak muscles.
	Very rare	Exacerbation of myasthenia gravis, of Lambert-Eaton syndrome or of advanced Duchenne's muscular dystrophy.
Breast and reproductive organs	Uncommon	Erectile dysfunction.
	Rare	Gynaecomastia in the long-term treatment of elderly patients: Experience to date indicates that this condition resolves when Isoptin is discontinued.
	Very rare	Elevation of prolactin levels, galactorrhoea.
General	Common	Headache.

Note: In patients with pacemakers, the pacing and sensing threshold may be raised while on verapamil hydrochloride treatment.

Overdosage

Symptoms of overdose: Toxicity symptoms after verapamil hydrochloride poisoning will depend on the amount taken, the time at which countermeasures are initiated and myocardial contractility (age-dependent). The following symptoms are observed in severe cases of verapamil poisoning: Severe drop in blood pressure, heart failure, bradycardia or tachycardia (e.g. junctional escape rhythm with AV dissociation and high-grade AV block) which can result in cardiovascular shock and cardiac arrest. Clouding of consciousness to the point of coma, hyperglycaemia, hypokalaemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema, impairment of kidney function and seizures. There have been occasional reports of deaths.

Treatment of overdosage: The main therapeutic aims are to achieve elimination of the compound and to re-instate stable cardiovascular function. The therapeutic measures to be taken will depend upon the time and mode of administration as well as the type and severity of the symptoms. In cases of poisoning with large quantities of prolonged-release formulations, it is important to note that the drug may be released and absorbed in the intestine for more than 48 hours after intake. Gastric lavage is advised after oral intoxication with verapamil hydrochloride, even if more than 12 hours have elapsed since ingestion, if no gastrointestinal motility (bowel sounds) is evident. If poisoning with prolonged-release products is suspected, extensive elimination measures are indicated, e.g. induced vomiting, gastric and small intestine drainage monitored by endoscopy, intestinal lavage, purgatives and high colonic enemas. Haemodialysis is not recommended as verapamil hydrochloride is not amenable to dialysis. Haemofiltration and, possibly, plasmapheresis (high plasma protein binding of calcium channel blockers) are, however, recommended. Standard emergency resuscitation measures, such as, closed chest cardiac massage, artificial respiration, defibrillation and/or pacemaker therapy are recommended.

Specific measures: Elimination of cardiodepressant effects, hypotension and bradycardia. Bradycardia is treated symptomatically by administering atropine and/or beta sympathomimetics (isoprenaline, orciprenaline). Life-threatening bradycardia requires short-term pacemaker therapy. Calcium is a specific antidote, e.g. 10 – 20 ml
of a 10% calcium gluconate solution intravenously (2.25 to 4.5 mmol), repeated as necessary or given by continuous infusion (e.g. 5 mmol/hour). Hypotension as a result of cardiogenic shock and arterial vasodilatation is treated with dopamine (up to 25 µg per kilogram of body weight per minute), dobutamine (up to 15 µg per kilogram of body weight per minute), epinephrine or noradrenaline. Dosing of these drugs depends solely on the response achieved. Serum calcium levels should be maintained at upper normal limits or slightly above. Owing to arterial dilatation, fluids should be substituted (Ringer's or saline solution) in the early stages of detoxification.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Verapamil hydrochloride belongs to the class of calcium antagonists. These substances have an inhibitory effect on the influx of calcium ions through muscle cell membranes. Verapamil hydrochloride exerts a calcium-antagonist effect on the smooth muscle, especially in the vessels and gastrointestinal tract. Its effect on the smooth muscles manifests as vasodilatation. As a calcium antagonist, verapamil hydrochloride also has a marked effect on the myocardium. Its effect on the AV node manifests as a prolongation of conduction time. A negative inotropic effect may arise in the working myocardium. In man, verapamil hydrochloride reduces total peripheral resistance as a result of vasodilatation without a reflex increase in cardiac output. This lowers the blood pressure accordingly.

Pharmacokinetic Properties

Following oral administration, 80% to 90% of the verapamil dose is rapidly absorbed from the small intestine. Owing to an extensive first pass metabolism bioavailability is only approximately 20 %. Peak plasma levels are achieved 1 to 2 hours after oral dosing. Plasma protein binding of verapamil hydrochloride is approximately 90%.

PHARMACEUTICAL PARTICULARS

Incompatibilities

Not applicable.

Special instructions for storage

Isoptin 80 mg: Do not store above 25°C.

Isoptin SR 240 mg: Do not store above 25°C. Store in the original pack.

Nature and contents of container

Isoptin 80 mg:
Original pack containing 20 film-coated tablets
Original pack containing 50 film-coated tablets
Original pack containing 100 film-coated tablets

Isoptin SR 240 mg:
Original pack containing 20 prolonged release tablets
Original pack containing 50 prolonged release tablets

Date of last revision
June 2007

THIS IS A MEDICAMENT

- Medicament is a product, which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

KEEP ALL MEDICAMENTS OUT OF REACH OF CHILDRENS

Council of Arab Health Ministers
Union of Arab Pharmacists

إن هذا دواء

- الدواء مستحضر يؤثر على صحتك ، وإستهلاكه خلافاً للتعليمات يعرضك للخطر .
- إتبع بدقة وخفة الطبيب وطريقة الإستعمال المنصوص عليها وتعليمات الصيدلي الذي صرفها لك .
- الطبيب والصيدلي هما الخبيران في الدواء وفي نفعه وضرره .
- لا تقطع مدة العلاج المحددة لك من تلقاء نفسك .
- لا تكرر صرف الدواء بدون وصفة طبية .

لا تترك الأدوية في متناول أيدي الأطفال .

مجلس وزراء الصحه العرب
واتحاد الصيادلة العرب

Abbott