SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Akilen 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film coated tablets containing 40mg of verapamil hydrochloride.

Excipients with known effect:

- Lactose. Each 40 mg film-coated tablet contains 40mg lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Very pale green, round, convex film-coated tablets, with diameter of core 7 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Prophylaxis and/or treatment of:

- Angina pectoris, including Prinzmetal's angina (coronary spasm, vasospastic angina).
- Supraventricular tachycardias such as paroxysmal supraventricular tachycardia, atrial fibrillation/flutter withrapid ventricular response (except in WPW syndrome, see "Contra-indications").
- Mild to moderate essential hypertension.

4.2. Posology and method of administration

The dose of verapamil hydrochloride should be adjusted individually in accordance with the severity of disease. Longstanding clinical experience shows that the average daily dose in all indications is between 240 mg and 360 mg. The daily dose should not exceed 480 mg on a long-term basis, although a higher dose may be used for a short period.

There is no limitation on the duration of use. Verapamil hydrochloride should not be discontinued abruptly after long-term use. It is recommended to taper the dosage.

Akilen 40 mg film-coated tablets should be used for patients likely to display a satisfactory response to low doses (e.g. patients with hepatic dysfunction or elderly patients). For patients

requiring higher dosages (e.g., 240 mg to 480 mg verapamil hydrochloride per day), formulations with a more suitable active drug content should be used.

Posology

Adults:

For the treatment of angina, including Prinzmetal's angina, the usual dose is 120 mg 3 to 4 times daily. Although 80 mg 3 times daily may be adequate in many patients with angina of effort, doses below 120 mg 3 times daily are unlikely to be effective in angina of rest and Prinzmetal's angina.

In cases of supraventricular tachycardia the usual dose is 40 mg to 120 mg 3 to 4 times daily according to the severity of the patient's condition.

For the treatment of essential hypertension the usual dose is 40 mg to 120 mg 3 to 4 times daily. In long-term treatment, a total daily dose of 480 mg should not be exceeded; short-term dose increases are possible only when directed by the physician.

Special Populations

Renal impairment

Currently available data are described in section 4.4. 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 section 4.4).

Method of administration

Tablets are for oral administration. The tablets should be swallowed whole with sufficient liquid, preferably with or shortly after meals.

Verapamil should not be taken with grapefruit juice (see section 4.5).

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Cardiogenic shock.

- Sick-sinus syndrome (bradycardia-tachycardia syndrome).
- Second-or third-degree AV block (except in patients with a functioning artificial pacemaker).
- Heart failure with reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mm Hg (unless secondary to a supraventricular tachycardia amenable to verapamil therapy).
- Simultaneous intravenous administration of beta-adrenergic blockers.
- 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.
- Use in pregnancy unless considered essential by the physician.
- Combination with ivabradine (see section 4.5).

4.4. Special warnings and precautions for use

Acute Myocardial infarction

Use with caution in acute myocardial infarction complicated by bradycardia, marked hypotension, or left ventricular dysfunction.

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 reduction in subsequent doses or discontinuation 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).

Patients with heart failure or those who are susceptible to heart failure should be fully digitalised before verapamil therapy as it may aggravate or precipitate cardiac failure.

Great care should be taken in: first degree AV block, bradycardia <50 beats/min, hypotension <90 mmHg systolic and ventricular tachycardias (QRS complex >0.12 sec).

If acute cardiovascular side effects arise, treat as for overdose (see section 4.9).

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.

Colchicine
There has been a single post marketing 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 section 4.5).

Digoxin
If verapamil is administered concomitantly with digoxin, reduce digoxin dosage (see section 4.5).

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
Intravenous verapamil hydrochloride often produces a decrease in blood pressure below baseline levels that is usually transient and asymptomatic but may result in dizziness.
HMG-CoA Reductase Inhibitors (“Statins”) – See section 4.5.

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).
Respiratory standstill has been reported for one patient with progressive muscular dystrophy following administration of verapamil.

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 section 4.2).

Akilen 40 mg film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 metabolized 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.

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. When verapamil 120 mg immediate -release was co-administered one hour before a single dose of dabigatran etexilate, the dabigatran Cmax was increased by about 180% and AUC by about 150%. No meaningful interaction was observed when verapamil was administered 2 hours after dabigatran etexilate (increase of Cmax by about 10% and AUC by about 20%).

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.

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

Antihypertensives, diuretics, vasodilators
Potentiation of the hypotensive effect.

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 blocking agents
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.

Aspirin
Increased tendency to bleed.

Ethanol (alcohol)
Elevation of ethanol plasma levels.

HMG Co-A Reductase Inhibitors ("Statins")
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.

Fluvastatin, pravastatin and rosuvastatin are not metabolized by CYP3A4 and are less likely to interact with verapamil.
Co-administration of verapamil with metformin may reduce the efficacy of metformin.

The following table provides a list of potential drug interactions with verapamil:

Concomitant drug	**Potential effect on verapamil or concomitant drug**	**Comment**
Alpha blockers		
Prazosin	↑ Prazosin Cmax (~40%) with no effect on half-life	Additive hypotensive effect.
Terazosin	↑ Terazosin AUC (~24%) and Cmax (~25%)	
Antiarrhythmics		
Flecainide	Minimal effect on flecainide plasma clearance (<~10%); no effect on verapamil plasma clearance	See additional information.
Quinidine	↓ Oral quinidine clearance (~35%)	Hypotension. 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. This may produce carbamazepine side effects such as diplopia, headache, ataxia or dizziness.
Phenytoin	↓ Verapamil plasma concentrations	
Antidepressants		

Concomitant drug	Potential effect on verapamil or concomitant drug	Comment
Imipramine	↑ Imipramine AUC (~15%)	No effect on level of active metabolite, desipramine.
Antidiabetics		
Glyburide	↑ Glyburide Cmax (~28%), AUC (~26%)	
Anti-gout		
Colchicine	Possible ↑ colchicine levels ↑ Colchicine AUC (~2.0fold) and Cmax (~1.3fold)	Reduce colchicine dose (see colchicine label).
Anti-infectives		
Clarithromycin	Possible ↑ in verapamil levels	
Erythromycin	Possible ↑ in verapamil levels	
Rifampicin	↓ Verapamil AUC (~97%), Cmax (~94%), oral bioavailability (~92%) with oral verapamil administration	Blood pressure lowering effect may be reduced.
Telithromycin	Possible ↑ in verapamil levels	
Antineoplastics		
Doxorubicin	↑ Doxorubicin AUC (104%) and Cmax (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, Cmax by ~3.4-fold	
Midazolam	↑ Midazolam AUC (~3fold) and Cmax (~2-fold)	
Beta blockers		

Concomitant drug	Potential effect on verapamil or concomitant drug	Comment
Metoprolol	↑ Metoprolol AUC (~32.5%) and Cmax (~41%) in angina patients	See section 4.4.
Propranolol	↑ Propranolol AUC (~65%) and Cmax (~94%) in angina patients	
Cardiac glycosides		
Digitoxin	↓ Digitoxin total body clearance (~27%) and extrarenal clearance (~29%)	
Digoxin	Healthy subjects: ↑ Digoxin Cmax (~44%) ↑ Digoxin C12h (~53%) ↑ Css by ~42% and ↑ AUC (50%)	
H2 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		
Ciclosporin	↑ ciclosporin AUC, Css, Cmax by ~45%	
Everolimus	Everolimus: ↑ AUC (~3.5fold) and ↑ Cmax (~2.3fold) Verapamil: ↑ Ctrough (~2.3-fold)	Concentration determinations and dose adjustments of everolimus may be necessary.
Sirolimus	Sirolimus ↑ AUC (~2.2fold); 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 Increase verapamil AUC (~43%)	See additional information.
Lovastatin	Possible ↑ lovastatin levels ↑ verapamil AUC (~63%) and Cmax (~32%)	
Simvastatin	↑ Simvastatin AUC (~2.6fold),	

Concomitant drug	Potential effect on verapamil or concomitant drug	Comment
	Cmax(~4.6-fold)	
Serotonin receptor antagonists		
Almotriptan	↑ Almotriptan AUC (~20%) ↑ Cmax (~24%)	
Uricosurics		
Sulfinpyrazone	↑ Verapamil oral clearance (~3-fold) ↓ bioavailability (~60%)	Blood pressure lowering effect may be reduced.
	No change in PK with intravenous verapamil administration	
Other		
Grapefruit juice	↑ R-(~49%) and S(~37%) verapamil AUC ↑ R-(~75%) and S(~51%) verapamil Cmax	Elimination half-life and renal clearance not affected. Grapefruit juice should therefore not be ingested with verapamil.
St. John's Wort	↓ R-(~78%) and S(~80%) verapamil AUC with corresponding reductions in Cmax	

4.6. Fertility, pregnancy and lactation

Pregnancy

Teratogenic Effects

There are no adequate and well-controlled study data in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Because animal reproduction studies are not always predictive of human response, during pregnancy (especially in the first trimester), verapamil should only be used if considered essential by the physician.

Breast-feeding

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) and that verapamil use may be compatible with breastfeeding.
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.

4.7. Effects on ability to drive and use machines

Due to its antihypertensive effect, depending on the individual response, verapamil hydrochloride may affect the ability to react to the point of impairing 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.

4.8. Undesirable effects

The following adverse events reactions have been reported with verapamil from clinical studies, post marketing 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 ADRs were:

- headache,
- dizziness,
- gastrointestinal disorders: nausea, constipation and abdominal pain,
- bradycardia,
- tachycardia,
- palpitations,
- hypotension,
- flushing,

- edema peripheral,
- fatigue.

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

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known**
Immune system disorders				Hypersensitivity
Nervous system disorders	Dizziness Headache		Paresthesia Tremor	Extrapyramidal disorder Paralysis (tetraparesis)[1] Seizures
Metabolism and nutrition disorders				Hyperkalaemia
Psychiatric disorders			Somnolence	Nervousness
Ear and labyrinth disorders			Tinnitus	Vertigo
Cardiac disorders	Bradycardia	Palpitations Tachycardia		Atrioventricular block (1°, 2°, 3°) Cardiac failure Cardiac arrest Brady arrhythmia Sinus arrest Sinus bradycardia Asystole
Vascular disorders	Flushing Hypotension			Vasodilation Erythromelalgia
Respiratory, thoracic and mediastinal				Bronchospasm Dyspnea

MedDRA System Organ Class	**Common**	**Uncommon**	**Rare**	**Not known**
disorders				
Gastrointestinal disorders	Constipation Nausea	Abdominal pain	Vomiting	Abdominal discomfort Gingival hyperplasia Ileus
Skin and subcutaneous tissue disorders			Hyperhidrosis	Angioedema Stevens-Johnson syndrome Erythema multiforme Alopecia Itching Pruritus Purpura Rash maculopapular Urticaria Rash Erythema
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	Edema peripheral	Fatigue		

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
site conditions				
Investigations				Blood prolactin increased Transaminases increased Blood alkaline phosphatase increased Hepatic enzymes increased

[1]There has been a single post marketing 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. See Interactions with other medicinal products and other forms of interaction section.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 national reporting system:

The Medicines Authority,
Post-Licensing Directorate,
203 Level 3, Rue D'Argens, GŻR-1368 Gżira
website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

4.9. Overdose

Symptoms

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

The usual intensive care measures should be taken. Fatalities have occurred as a result of overdose. Verapamil hydrochloride cannot be removed by hemodialysis.

The specific antidote is calcium, e.g. 10-20 ml in a 10% calcium gluconate solution administered intravenously (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 the case of 2 or 3 degree AV block, sinus bradycardia, asystole: Atropine, isoprenaline, orciprenaline or pacemaker therapy. Asystole should be handled by the usual measures including beta adrenergic stimulation (e.g., isoproterenol hydrochloride).
- In the case of hypotension: Dopamine, dobutamine, norepinephrine.
- If there are any signs of continuing myocardial failure: Dopamine, dobutamine, if necessary repeated calcium injections, and possibly other medication that increases cardiac contractility combined with isoprenaline.

5. PHARMACOLOGICAL PROPERTIES

5.1. 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, 4dimethoxyphenyl) ethyl}methylaminol] propyl]-3, 4-dimethoxy-α-(1-methylethyl) hydrochloride.

It has a molecular weight of 491.07 and the molecular formula is C27H38N204 x HCl.

<u>Mechanism of action and Pharmacodynamic effects</u>

Verapamil inhibits the transmembrane influx of calcium ions into the heart and vascular smooth muscle cell. The myocardial oxygen demand is lowered directly as a result of the effect on the energy consuming metabolic processes of the myocardial cell and indirectly due to a reduction of the afterload.

Due to its effect on coronary vascular smooth muscle, verapamil enhances myocardial blood flow, even in post stenotic areas, and relieves coronary spasms.

These properties contribute to the anti-ischemic and antianginal efficacy of verapamil in all types of coronary artery disease.

Verapamil has a marked antiarrhythmic effect, particularly in supraventricular arrhythmias. It delays impulse conduction in the AV node. Owing to this, sinus rhythm is restored and/or ventricular rate is normalized, depending on the type of arrhythmia. Normally, the rate is either not affected or only minimally lowered.
The antihypertensive effect of verapamil stems from a decrease in peripheral vascular resistance, without an increase in heart rate as a reflex response. As early as day 1 of treatment, blood pressure falls; the effect is found to persist also in long-term therapy.

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. Nor-verapamil 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 nor-verapamil 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 one to two hours after IR administration, and four to five hours after SR administration. The peak plasma concentration of nor-verapamil is attained approximately one and five hours after IR or SR administration, respectively. The presence of food has no effect on the bioavailability of verapamil.
Half-life values between 3 and 7 hours have been measured for the elimination of unchanged substance from the plasma after single intravenous and oral administration.

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 nor-verapamil has any appreciable pharmacological effect (approximately 20% that of the parent compound), which was observed in a study with dogs.
In coronary heart disease and hypertension, no correlation was found between the therapeutic effect and the plasma concentration; a definite correlation with the plasma level was determined only for the effect on the PR interval. The concentration curve of verapamil in the plasma is protracted after administration of the sustained-release formulations, and is also flatter and more homogenous than after administration of the instant release formulations.

Elimination

Following intravenous infusion, verapamil is eliminated bi-exponentially, with a rapid early distribution phase (half-life about four minutes) and a slower terminal elimination phase (half-life two to five hours). 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

Paediatric population

Limited information on the pharmacokinetics in the pediatric population is available. After intravenous dosing, the mean half-life of verapamil was 9.17 hours and the mean clearance was 30 L/h, whereas it is around 70 L/h for a 70-kg adult. Steady-state plasma concentrations appear to be somewhat lower in the pediatric population after oral dosing compared to those observed in adults.

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 nor-verapamil 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.

Verapamil hydrochloride, administered intravenously, has been shown to be rapidly metabolized.

5.3. 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.

The cardiovascular findings and the diffuse gingival hyperplasia seen in the chronic toxicity of verapamil hydrochloride are taken into account in section 4.8.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Lactose monohydrate
- Croscarmellose sodium
- Cellulose microcrystalline
- Silica colloidal anhydrous
- Magnesium stearate
- Polyethylene glycol 6000
- Opadry green OY-3875H (Hypromellose (E464), titanium dioxide (E171), macrogol/polyethylene glycol 400, indigo carmine aluminium lake (E132), iron oxide yellow (E172), iron oxide black (E172)).

6.2. Incompatibilities

None known.

6.3. Shelf life

5 years

6.4. Special precautions for storage

Store below 25ºC in the original packaging in order to protect from light.

6.5. Nature and contents of container

Combination polyvinylchloride film and aluminium foil blisters of ten tablets.
Blisters are placed, with a patient information leaflet, in a card carton. Packs of 50, 100, 250, 500 and 1000 tablets are available.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Medochemie Ltd, 1-10 Constantinoupoleos street, 3011 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER

MA032/03801

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28.12.2006 / 05.07.2012

10. DATE OF REVISION OF THE TEXT

11/2021