SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CORDAMIL 40 mg film-coated tablets
CORDAMIL 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CORDAMIL 40 mg

Each film-coated tablet contains 40 mg verapamil hydrochloride.

Excipients: lactose monohydrate 35.60 mg, tartrazine (E 102) 0.002 mg.

CORDAMIL 80 mg

Each film-coated tablet contains 80 mg verapamil hydrochloride.
Excipients: lactose monohydrate 71.20 mg, tartrazine (E 102) 0.015 mg.

For the list of all excipients, see point 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

CORDAMIL 40 mg
Film-coated, light yellow lenticular tablets with a uniform appearance, compact and homogeneous structure, intact edges, engraved on one of the sides "V 40", with a diameter of 7 mm.

CORDAMIL 80 mg
Film-coated tablets, yellow lenticular with uniform appearance, compact and homogeneous structure, intact edges, engraved with "V 80" on one side and breaking line on the other, with a diameter of 9 mm.
The breaking line is intended to ease swallowing of the tablet and not for dose modification (equivalence of the two parts was not demonstrated).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of coronary heart disease, including:
- chronic stable angina pectoris (effort angina),

- unstable angina pectoris:
    - aggravated angina, resting angina, vasospastic angina (Prinzmetal angina),
    - post heart-attack angina in patients without heart failure, when- adrenergic beta-blockers are contraindicated.

Prevention of ventricular fast heart rate disorders not controlled by tonic-cardiac glycosides or beta-blocker (for example supraventricular paroxysmal tachycardia, atrial fibrillation/flutter with rapid ventricular response, except for Wolff-Parkinson-White syndrome).

Moderate to mild essential hypertension.

4.2 Posology and method of administration

The dose of verapamil hydrochloride should be adjusted individually according to the severity of the condition. Long-term clinical experience demonstrates that the average dose for all indications is in the dose range of 240 mg-360 mg.

The maximum daily dose should not exceed 480 mg for long-term treatment; in the case of short-term treatment, a higher dose may be administered.

Verapamil treatment should not be stopped abruptly. Gradual dose reduction is recommended.

The pharmaceutical form with a concentration of 40 mg of verapamil hydrochloride is recommended for patients who require low doses (e.g. patients with liver disease and elderly patients).

For patients requiring higher doses (360 to 480 mg of verapamil hydrochloride per day), other formulations with appropriate concentrations of the active substance should be administered.

Adolescents and children
Adolescents aged 14 and above with body weight over 50 kg

Coronary heart disease, paroxysmal supraventricular tachycardia, atrial fibrillation and atrial flutter.
The recommended dose is 120-480 mg verapamil hydrochloride, given in 3-4 doses.

Hypertension
The recommended dose is 120-480 mg verapamil hydrochloride, taken in 3 doses.

Children aged 6-14 years (only for heart rhythm disorders)

The recommended dose is 80-360 mg verapamil hydrochloride, taken in 2-4 doses.

Liver failure
Depending on the severity of the liver damage, the metabolism of verapamil hydrochloride is delayed, which intensifies its effects. Therefore, in this group of patients the dose should be adjusted and treatment should be initiated with the minimum effective dose.

Administration method
The tablets should be swallowed whole, with liquid, preferably during a meal or immediately after a meal.
For ease of swallowing, the tablets can be broken into two and the two halves swallowed as one dose.

4.3 Contraindications
Hypersensitivity to the active substance(s) or to any of the excipients listed in point 6.1;
Cardiogenic shock;
Acute myocardial infarction with complications;
Grade II and III AV block, except for patients with functional pacemaker;
Sinus node disease, except for patients with functional pacemaker;
Congestive heart failure;
Bradycardia with a frequency <50 beats per minute;
Hypotension (systolic blood pressure <90 mmHg);
Atrial fibrillation/atrial flutter, associated with Wolff-Parkinson-White syndrome.

4.4 Special warnings and precautions for use

Careful administration and careful monitoring are recommended in the following cases:
- first degree AV block;
- hypotension;
- bradycardia;
- hepatic impairment (see point 4.2);
- neuromuscular transmission disorders (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

Cordamil contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Contains tartrazine (E 102). May cause allergic reactions.

4.5 Interactions with other drugs and other forms of interaction

In vitro metabolic studies have shown that verapamil is metabolised by the cytochrome CYP3A4 P450, CYP1A2, CYP2C8, CYP2C9 and CYP2C18 enzymes. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes.
Significant clinical interactions with CYP3A4 inhibitors have been reported leading to increased plasma concentrations of verapamil hydrochloride, while inducers of CYP3A4 have resulted in decreased plasma concentrations of verapamil hydrochloride, therefore patients should be monitored for interactions.

The following table presents a list of possible medicine interactions based on pharmacokinetic properties:

Potential interactions associated with verapamil administration

Medicines administered in combination	**Possible effects of other medicines on verapamil and effects of verapamil on other medicines**	**Comments**
Alpha-blockers		
Prazosin	Increases prazosin Cmax (approximately 40%) with no effect on elimination half-life	Additional hypotensive effect
Terazosin	Increases terazosin AUC (by about 24%) and Cmax— (by about 25%)	
Acetylsalicylic acid		Increased tendency to bleed
Ethyl alcohol	Increases plasma concentrations of ethyl alcohol	
ANTIARRHYTHMICS		
Flecainide	Minimal effect on flecainide plasma clearance (approximately 10%); the plasma clearance of verapamil is not affected	Hypotension Pulmonary edema may occur in patients with obstructive hypertrophic cardiomyopathy
Quinidine	Decreases quinidine clearance (approximately 35%)	
Antihistamines		

Theophylline	Decreases theophylline clearance (approximately 20%)	In smokers, clearance has been reduced to a lesser extent
Anticonvulsants		
Carbamazepine	Increases the AUC of carbamazepine (approximately 46%) in patients with seizures who do not fully respond to treatment. Elevated carbamazepine plasma concentrations.	Increases plasma concentrations of carbamazepine; this may cause side effects of carbamazepine, such as diplopia, headache, ataxia and dizziness.
Antidepressants		
Imipramine	Increases the AUC of imipramine (by about 15%)	No effect on the plasma concentrations of the active metabolite, desipramine
Oral antidiabetics		
Glyburide	Increases glyburide AUC (by about 26%) and Cmax (by about 28%)	
Antibiotics		
Erythromycin	Possibly increases the plasma concentrations of verapamil	
Rifampicin	Decreases AUC (approximately 97%), Cmax (approximately 94%) and oral bioavailability (approximately 92%) of verapamil	The hypotensive effect can be reduced
Telithromycin	Possibly increases the plasma concentrations of verapamil	
Antihypertensives, diuretics, vasodilators		
	Potentiation of the hypotensive effect	
Antineoplastics		
Doxorubicin	Increased AUC (approximately 89%) and Cmax (approximately 61%) of doxorubicin	In patients with small cell lung carcinoma
Antiretrovirals		
Ritonavir	Increased plasma concentrations of verapamil with some of the	

	antiretroviral medicines used in HIV infection, such as ritonavir, due to the metabolic inhibitory potential of the antiviral medicines.	
Barbiturates		
Phenobarbital	Increases the plasma clearance of verapamil by approximately 5 times	
Benzodiazepines and other anxiolytics		
Buspirone	Increases the AUC and Cmax of buspirone approximately 3 and 4 times, respectively.	
Midazolam	Increases the AUC and Cmax of midazolam about 3 times and 2 times, respectively.	
Beta blockers		
Metoprolol	In patients with angina pectoris, the AUC and Cmax of metoprolol increase by approximately 32.5% and 41%, respectively.	
Propranolol	In patients with angina pectoris, the AUC and Cmax of propranolol increase by approximately 65% and 94%, respectively.	
Antiarrhythmics, beta-blockers	Increases the AUC of antiarrhythmics and beta-blockers (by about 24%)	Reciprocal exacerbation of cardiovascular effects (worsening of AV block, worsening of heart rate, occurrence of heart failure, worsening of hypotension)
Intravenous beta-blockers	Intravenous beta-blockers should not be used in patients receiving verapamil hydrochloride (except those in intensive care units).	
Inhalation anesthetics		

		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).
Neuromuscular blockers		
	The effects of neuromuscular blockers can be amplified	
Cardiotonic glycosides		
Digoxin	Decreases the total clearance of digoxin (by about 27%). In healthy subjects: Cmax increases by approximately 45-53%, plasma concentration increases at steady state by approximately 42%, AUC increases by approximately 52%.	
H2-histaminergic blockers		
Cimetidine	Increase the AUC of R-verapamil (by about 25%) and S-verapamil (by about 40%); decrease the clearance of R-verapamil and S-verapamil.	
Immunosuppressive		
Cyclosporine	Increases the AUC of cyclosporine, increases the steady-state plasma concentration, Cmax by approximately 45%.	
Sirolimus	Possibly increases the plasma concentrations of sirolimus.	
Tacrolimus	Possibly increases the plasma concentrations of tacrolimus.	
Lipid Lowering		

Atorvastatin	Possibly increases the plasma concentrations of atorvastatin.	
Lovastatin	Possibly increases the plasma concentrations of lovastatin.	
Simvastatin	Increased AUC and Cmax of simvastatin approximately 2.6 times and 4.6 times, respectively.	
Serotonin antagonists		
Almotriptan	Almotriptan AUC and Cmax increase by approximately 20% and 24%, respectively.	
Uricosuric		
Sulfinpyrazone	Increases the clearance of verapamil 3 times, decreases bioavailability by approximately 60%.	The hypotensive effect of verapamil may be reduced
Mood stabilizers		
Lithium	Increases the neurotoxicity of lithium	
Others		
Grapefruit juice	Increase the AUC of R-verapamil (by about 49%) and of S-verapamil (by about 37%); increase the Cmax of R-verapamil (by about 75%) and of S-verapamil (by about 51%). The elimination half-life and renal clearance do not change.	
Herbal preparations containing St. John's wort (*Hypericum perforatum)*		
	Decrease the AUC of R-verapamil (by about 78%) and of S-verapamil (by about 80%) with corresponding reductions in Cmax.	

HMG-CoA reductase inhibitors ("Statins")

Treatment with HMG-CoA reductase inhibitors (e.g. simvastatin/lovastatin) in patients receiving verapamil should be started with the lowest effective dose and gradually increased. A decrease in statin dose and readjustment, depending on plasma cholesterol levels, should be considered if verapamil treatment is added to patients receiving or already using HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin or lovastatin).

There are no direct *in vivo* clinical data on the interaction between atorvastatin and verapamil. However, verapamil is highly likely to influence the pharmacokinetic properties of atorvastatin and, to the same extent, of simvastatin and lovastatin.

Precautions should be taken when co-administering atorvastatin with verapamil.

Fluvastatin, pravastatin and rosuvastatin are not metabolised by CYP3A4 and their interaction with verapamil is unlikely.

4.6 Fertility, pregnancy and lactation

No data are available on the use of verapamil in pregnant women.
Verapamil should be used during pregnancy only if absolutely necessary.
Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.
Verapamil is excreted in human milk.
There is evidence that verapamil increases prolactin secretion and may increase galactorrhea in isolated cases.
Breast-feeding should be discontinued during treatment with verapamil.

4.7 Effects on ability to drive and use machines

Depending on the response to treatment, verapamil hydrochloride may affect the ability to react to the extent that the ability to drive, use machines or perform dangerous tasks may be affected. This situation occurs especially at the start of treatment, when the dose is increased, in case of switching from another treatment to treatment with verapamil or in case of combination with ethyl alcohol.

4.8 Adverse reactions

Reported adverse reactions were classified by apparatus, systems and organs and by frequency. Frequency is defined using the following convention: very common (> 1/10), frequent (> 1/100 and <1/10); uncommon (> 1/1000 and <1/100); rare (> 1/10000 and <1/1000); very rare (</10000); with unknown frequency (which cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing gravity.

Classification by apparatus, systems and organs	**Frequency**	**Adverse reaction**
Immune system disorders	Unknown	Hypersensitivity reactions
Nervous system disorders	Unknown	Headaches dizziness Paresthesia, Tremor, Extrapyramidal disorders
Acoustic and vestibular disorders	Unknown	Vertigo, Tinnitus
Heart disorders	Unknown	Block AV grade I, II, III Sinus bradycardia, Heart attack, Peripheral edema, Palpitations, Tachycardia, Heart failure
Vascular disorders	Unknown	Hypotension, Hot flashes
Gastrointestinal disorders	Unknown	Nausea, Vomiting, Constipation, Ileus, Gingival hyperplasia, Abdominal pain/discomfort
Skin and subcutaneous tissue disorders	Unknown	Angioedema Stevens-Johnson syndrome, Polymorphic erythema, Transient maculopapular erythema Urticaria Purpura Pruritus Alopecia
Musculoskeletal and connective tissue disorders	Unknown	Muscle weakness Myalgia Arthralgia
Disorders of the genital tract and breast	Unknown	Impotence Gynecomastia Galactorrhoea
General disorders and administration place level	Unknown	Fatigue
Diagnostic investigations	Unknown	Increased serum liver enzymes, Increased prolactinemia

Reporting suspected adverse reactions

Reporting suspected side effects after authorization of the medicine is important. This allows continuous monitoring of the benefit/risk ratio of the medicine. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Symptoms
Hypotension, heart failure, bradycardia-tachycardia arrhythmias, up to high-grade AV block and sinoatrial block, stupor and metabolic acidosis have been reported.
Deaths have been reported as a result of overdose.

Treatment
Treatment for overdose with verapamil hydrochloride should be primarily to support vital functions. Parenteral calcium administration, beta adrenergic stimulation and gastrointestinal lavage have been used in the treatment of verapamil overdose. Patients should be supervised and hospitalized for up to 48 hours, due to the possibility of prolonged absorption, in the case of slow-release dosage forms.
Verapamil hydrochloride cannot be dialyzed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective calcium channel blockers, calcium blockers with direct cardiac effects, phenylalkylamines, ATC code CO8DA01.
Verapamil hydrochloride blocks the trans-membrane influx of calcium ions into myocardial cells and smooth muscle vessels. It decreases myocardial oxygen demand by directly intervening in metabolic processes that consume myocardial energy and indirectly by reducing cardiac load. The blocking effect of calcium channels on the smooth muscles of the coronary arteries increases the irrigation of the myocardium, even in the areas of post-stenosis and relieves coronary spasm. The antihypertensive action of verapamil is based on the decrease of peripheral vascular resistance, without reflex tachycardia.
Verapamil hydrochloride has a marked antiarrhythmic effect, especially in supraventricular arrhythmias. It delays conduction in the atrioventricular node. The result, depending on the type of arrhythmia, is the restoration of sinus heart rate and/or normalization of ventricular rate. The normal frequency of heart contractions is not affected, or is slightly decreased.

5.2 Pharmacokinetic properties

Verapamil hydrochloride is rapidly absorbed in the small intestine. Absorption is 90-92%. Peak plasma concentrations of verapamil are reached 1-2 hours after administration of the prolonged-release form. The plasma half-life is 3-7 hours. Verapamil is approximately 90% bound to plasma proteins.
The mean systemic bioavailability of verapamil after a single dose is approximately 22% due to extensive hepatic metabolism on first pass. Bioavailability is 1.5 to 2 times higher with repeated administration. In patients with cirrhosis of the liver, a considerable increase in systemic bioavailability is expected.
The substance is metabolized to a large extent. In humans, a large number of metabolites were identified, of which 12 were identified.
Verapamil is extensively metabolized. 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.
Verapamil and its metabolites are mainly eliminated by the kidney. Only 3-4% of the dose is eliminated unchanged. A proportion of 50% of the dose is eliminated by the kidneys in 24 hours and 70% in 5 days. Up to 16% of the dose is excreted in the faeces. Renal dysfunction has no effect on the pharmacokinetics of verapamil, as shown in comparative studies that included patients with end-stage renal disease and subjects with healthy kidneys. The elimination half-life is prolonged in patients with cirrhosis of the liver due to low oral clearance and higher volume of distribution.

5.3 Preclinical safety data

Single dose toxicity (acute toxicity)
Toxicity testing after a single dose of verapamil hydrochloride was performed in different animal species.
The mean single dose toxicity (LD50 in mg/kg) was:

	i.v.	**i.p.**	**s.c.**	**p.o.**
rat	**16**	**67**	**107**	**114**
mouse	**8**	**68**	**68**	**163**
Guinea pig	**-**	**-**	**-**	**140**

LD50 (lethal dose 50) in the conventional sense is the dose calculated to cause the death of 50% of exposed animals.

Repeated dose toxicity (chronic subchronic toxicity)

Chronic subchronic toxicity studies were performed in rats and dogs. At high doses (> 30 mg/kg), verapamil hydrochloride caused lenticular changes and/or suture and cataract line injuries in hunting dogs. These changes were not observed in any other animal species. No cases of cataracts have been reported in humans to date, with the etiology of verapamil hydrochloride.

Mutagenicity and carcinogenesis
In vitro and *in vivo* studies have shown no evidence of mutagenic potential of verapamil hydrochloride.
A long-term study in rats did not show any evidence of the carcinogenic potential of verapamil hydrochloride.

Reproductive toxicity
Embryotoxicity studies in two animal species did not show any evidence of teratogenic potential at daily doses of up to 15 mg/kg in rabbits and 60 mg/kg in rats. However, in rats, this dose, which is already in the range of toxic doses to females, has caused embryotoxic effects (mortality, delayed growth).

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Core
Lactose monohydrate
Maize starch
Povidone K 30
Sodium starch glycolate
Talc
Magnesium stearate
Colloidal silica anhydrous

Tablet coating
Hypromellose
Titanium dioxide (E 171)
Macrogol 6000
Talc
Tartrazine (E 102)

6.2 Incompatibility

This medicinal product must not be mixed with other medicinal products.

6.3 Period of validity

The expiry date is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C in the original package.

6.5 Nature and contents of package

Box of 30 or 60 film-coated tablets, packed in PVC/Al blisters of 10 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

TRUSTPHARM LTD.
50 Hakishon Street, Tel-Aviv

8. MANUFACTURER

S.C. AC HELCOR S.R.L.
50 Dr. Victor Babeş Street, 430092, Baia Mare
Romania

9. MARKETING AUTHORIZATION NUMBER

CORDAMIL 40 mg: 169-31-36504-99
CORDAMIL 80 mg: 168-85-36505-99

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