SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Verapress 240 SR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains Verapamil Hydrochloride 240 mg

Excipient with known effect:

Each caplet contains approximately 35 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Caplets.

Light green, film coated, caplets, scored on both sides.

The caplet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of mild to moderate hypertension.
The treatment and prophylaxis of angina pectoris.

4.2 Posology and method of administration

Verapress 240 SR should be administered with food. Verapress 240 SR caplets can be divided. They should not be chewed, sucked or crushed.

Hypertension

One caplet of Verapress 240 SR daily. For patients new to verapamil therapy, the physician should consider halving the initial dose to 120 mg (half Verapress 240 SR). Most patients respond to 240 mg daily (one caplet Verapress 240 SR) given as a single dose. If control is not achieved after a period of at least one week, the dosage may be increased to a maximum of two Verapress 240 SR caplets daily (one in the morning and one in the evening at an interval of about twelve hours). A further reduction in blood pressure may be achieved by combining Verapress 240 SR with other antihypertensive agents, in particular diuretics. Half Verapress 240 SR may be used for dose titration purposes.

Angina Pectoris

- One caplet of Verapress SR daily. For patients new to verapamil therapy, the physician should consider halving the initial dose to 120 mg (half Verapress 240 SR).
- Most patients respond to 240 mg daily (one caplet Verapress 240 SR) given as a single dose. If control is not achieved after a period of at least one week, the dosage may be increased to a maximum of two Verapress 240 SR caplets daily (one in the morning and one in the evening at an interval of about twelve hours).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.

Cardiogenic shock; acute myocardial infarction complicated by bradycardia, marked hypotension or left ventricular failure; second or third degree atrioventricular (AV) block (except in patients with a functioning artificial pacemaker); sino-atrial block; sick sinus syndrome (except in patients with a functioning artificial pacemaker); uncompensated heart failure; bradycardia of less than 50 beats/minute; hypotension of less than 90 mmHg systolic.

Patients with atrial flutter/fibrillation in the presence of an accessory pathway (*e.g.* WPW syndrome) may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.

Combination with ivabradine (see section 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Since verapamil is extensively metabolized in the liver, careful dose titration is required in patients with liver disease.
Although the pharmacokinetics of verapamil in patients with renal impairment are not affected, caution should be exercised and careful patient monitoring is recommended. Verapamil is not removed during dialysis.

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 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 section 4.8 “Undesirable Effects”.

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.

Caution should be exercised in treatment with HMG CoA reductase inhibitors (e.g., simvastatin, atorvastatin or lovastatin) for patients taking verapamil. These patients should be started at the lowest possible dose of verapamil and titrated upwards. If verapamil treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g., simvastatin, atorvastatin or lovastatin), refer to advice in the respective statin product information.

Use with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

Sodium

This medicinal product contains approximately 35 mg sodium per caplet, which is equivalent to 1.75% of the WHO recommended maximum daily intake of 2 g for an adult.

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 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. Coadministration 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 are potential drug interactions associated due to pharmacokinetic reasons:

Acetylsalicylic acid

Concomitant use of verapamil with aspirin may increase the risk of bleeding

Alcohol

Increase in blood *alcohol* has been reported.

Alpha blockers

Verapamil may increase the plasma concentrations of *prazosin* and *terazosin* which may have an additive hypotensive effect.

Antiarrhythmics

Verapamil may slightly decrease the plasma clearance of *flecainide* whereas *flecainide* has no effect on the verapamil plasma clearance.

Verapamil may increase the plasma concentrations of *quinidine*. Pulmonary oedema may occur in patients with hypertrophic cardiomyopathy

The combination of verapamil and *antiarrhythmic agents* may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Anticonvulsants

Verapamil may increase the plasma concentrations of *carbamazepine.* This may produce side effects such as diplopia, headache, ataxia or dizziness. *Phenytoin* may decrease the plasma concentrations of verapamil.

Antidepressants

Verapamil may increase the plasma concentrations of *imipramine*.

Antidiabetics

Verapamil may increase the plasma concentrations of *glibenclamide (glyburide)*. Co-administration of verapamil with metformin may reduce the efficacy of metformin.

Antihypertensives, diuretics, vasodilators

Potentiation of the hypotensive effect.

Anti-infectives

Rifampicin may reduce the plasma concentrations of verapamil which may produce a reduced blood pressure lowering effect. When verapamil and rifampicin are administrated together there is no change in PK. *Erythromycin, clarithromycin* and *telithromycin* may increase the plasma concentrations of verapamil.

Antineoplastics

Verapamil may increase the plasma concentrations of *doxorubicin.*

Barbiturates

Phenobarbital may reduce the plasma concentrations of verapamil.

Benzodiazepines and other anxiolytics

Verapamil may increase the plasma concentrations of *buspirone* and *midazolam*.

Beta blockers

Verapamil may increase the plasma concentrations of *metoprolol* and *propranolol* which may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Intravenous *beta-blockers* should not be given to patients under treatment with verapamil.

Cardiac glycosides

Verapamil may increase the plasma concentrations of *digitoxin* and *digoxin*. Verapamil has been shown to increase the serum concentration of *digoxin* and caution should be exercised with regard to digitalis toxicity. The digitalis level should be determined and the glycoside dose reduced, if required.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Verapamil is known to inhibit CYP3A and P-gp. When verapamil and *colchicine* are administered together, inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to *colchicine*. Combined use is not recommended.

H_2 Receptor antagonists

Cimetidine may increase the plasma concentrations of verapamil.

HIV antiviral agents

Due to the metabolic inhibitory potential of some of the *HIV antiviral agents*, such as *ritonavir*, plasma concentrations of verapamil may increase. Caution should be used or dose of verapamil may be decreased.

Immunosuppressants

Verapamil may increase the plasma concentrations of *ciclosporin*, *everolimus, sirolimus* and *tacrolimus*.

Concentration determinations and dose adjustments of everolimus and sirolimus may be necessary.

Lipid lowering agents

Verapamil may increase the plasma concentrations *atorvastatin, lovastatin* and *simvastatin.*

Treatment with HMG *CoA reductase inhibitors* (e.g., *simvastatin, atorvastatin* or *lovastatin*) in a patient taking verapamil should be started at the lowest possible dose and titrated upwards. If verapamil treatment is to be added to patients already taking an *HMG CoA reductase inhibitor* (e.g., *simvastatin, atorvastatin* or *lovastatin*), consider a reduction in the statin dose and re-titrate against serum cholesterol concentrations.

Atorvastatin has been shown to increase verapamil levels. Although there is no direct in vivo clinical evidence, there is strong potential for verapamil to significantly affect *atorvastatin* pharmacokinetics in a similar manner to s*imvastatin* or *lovastatin.* Consider using caution when *atorvastatin* and verapamil are concomitantly administered.

Fluvastatin, pravastatin and *rosuvastatin* are not metabolized by CYP3A4 and are less likely to interact with verapamil.

Lithium

Serum levels of *lithium* may be reduced. However, there may be increased sensitivity to *lithium* causing enhanced neurotoxicity. Patients receiving both drugs should be monitored carefully.

Neuromuscular blocking agents employed in anaesthesia

The effects may be potentiated.

Serotonin receptor agonists

Verapamil may increase the plasma concentrations of *almotriptan*.

Theophylline

Verapamil may increase the plasma concentrations of *theophylline.*

Uricosurics

Sulfinpyrazone may reduce the plasma concentrations of verapamil which may produce a reduced blood pressure lowering effect. When verapamil and *sulfinpyrazone* are administrated together, there is no change in PK.

Anticoagulants

When oral verapamil was co-administered with dabigatran etexilate (150 mg), a P-gp substrate, the C_{max} and AUC of dabigatran were increased but magnitude of this change differs depending on time between administration and the formulation of verapamil. Co-administration of verapamil 240 mg extended-release at the same time as dabigatran etexilate resulted in increased dabigatran exposure (increase of C_{max} by about 90% and AUC by about 70%).

Close clinical surveillance is recommended when verapamil is combined with dabigatran etexilate and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

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 verapamil may need to be reduced (see DOAC label for dosing instruction).

Other Cardiac therapy

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

Other

St. John's Wort may reduce the plasma concentrations of verapamil, whereas *grapefruit juice* may increase the plasma concentrations of verapamil.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled study data in pregnant women. Although animal studies have not shown any teratogenic effects (see section 5.3), verapamil should not be given during the first trimester of pregnancy unless, in the clinician's judgement, it is essential for the welfare of the patient.

Verapamil hydrochloride is excreted in human breast milk. Limited human data from oral administration has shown that the infant relative dose of verapamil is low (0.1 - 1% of the mother's oral dose) and that verapamil use may be compatible with breastfeeding. Due to the potential for serious adverse reactions in nursing infants, verapamil should only be used during lactation if it is essential for the welfare of the mother

4.7 Effects on ability to drive and use machines

Depending on individual susceptibility, the patient's ability to drive a vehicle, operate machinery or work under hazardous conditions may be impaired. This is particularly true in the initial stages of treatment, when changing over from another drug, when the dose is raised or when taken in conjunction with alcohol. Like many other common medicines, verapamil has been shown to increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

4.8 Undesirable effects

Reactions from Post marketing Surveillance or Phase IV Clinical Trials

The following adverse events reported with verapamil are listed below by system organ class:

Immune system disorders: allergic reactions (e.g. erythema, pruritus, urticaria) are very rarely seen.

Nervous system disorders: headache, dizziness, paresthesia, tremor and extrapyramidal syndrome.

Ear and labyrinth disorders: vertigo and tinnitus.

Cardiac disorders/vascular disorders: bradycardic arrhythmias such as sinus bradycardia, sinus arrest with asystole, 2nd and 3nd degree AV block, bradyarrhythmia in atrial fibrillation, peripheral oedema, palpitations, tachycardia, development or aggravation of heart failure and hypotension. There have been rare reports of flushing.

Gastrointestinal disorders: nausea, vomiting, constipation, ileus and abdominal pain/discomfort. Gingival hyperplasia may occur very rarely when the drug is administered over prolonged periods, and is fully reversible when the drug is discontinued.

Skin and subcutaneous tissue disorders: ankle oedema, Quincke's oedema, Steven-Johnson syndrome, erythema multiforme, erythromelalgia, alopecia and purpura.

Musculoskeletal and connective tissue disorders: muscular weakness, myalgia and arthralgia.

Reproductive system and breast disorders: impotence (erectile dysfunction) has been rarely reported and isolated cases of galactorrhoea. On very rare occasions, gynaecomastia has been observed in elderly male patients under long-term verapamil treatment, and is fully reversible in all cases when the drug was discontinued.

General disorders and administration site conditions: fatigue.

Investigations: A reversible impairment of liver function characterized by an increase of transaminase and/or alkaline phosphatase may occur on very rare occasions during verapamil treatment and is most probably a hypersensitivity reaction. Rises in blood prolactin levels have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
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

The course of symptoms in verapamil intoxication depends on the amount taken, the point in time at which detoxification measures are taken and myocardial contractility (age-related). The main symptoms are as follows: blood pressure fall (at times to values not detectable), shock symptoms, loss of consciousness, 1st and 2nd degree AV block (frequently as Wenckebach's phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm, asystole, bradycardia up to high degree AV block and, sinus arrest, hyperglycaemia, stupor and metabolic acidosis and acute respiratory distress syndrome. Fatalities have occurred as a result of overdose.

The therapeutic measures to be taken depend on the point in time at which verapamil was taken and the type and severity of intoxication symptoms. In intoxications with large amounts of slow-release preparations, it should be

noted that the release of the active drug and the absorption in the intestine may take more than 48 hours. Verapamil hydrochloride cannot be removed by haemodialysis. Depending on the time of ingestion, it should be taken into account that there may be some lumps of incompletely dissolved caplets along the entire length of the gastrointestinal tract, which function as active drug depots.

General measures to be taken: Gastric lavage with the usual precautions, even later than 12 hours after ingestion, if no gastrointestinal motility (peristaltic sounds) is detectable. Where intoxication by Verapress 240 SR is suspected, extensive elimination measures are indicated, such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopy, intestinal lavage, laxative, high enemas. The usual intensive resuscitation measures apply, such as extrathoracic heart massage, respiration, defibrillation and/or pacemaker therapy.

Specific measures to be taken: Elimination of cardiodepressive effects, hypotension or bradycardia. The specific antidote is calcium, e.g. 10 -20 ml of 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 case of 2nd or 3rd degree AV block, sinus bradycardia, asystole - atropine, isoprenaline, orciprenaline or pacemaker therapy. In case of hypotension - dopamine, dobutamine, noradrenaline. If there are signs of continuing myocardial failure - dopamine, dobutamine, if necessary repeated calcium injections.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives.

ATC-Code: C08DA01

Verapamil, a phenylalkylamine calcium antagonist, has a balanced profile of cardiac and peripheral effects. It lowers heart rate, increases myocardial perfusion and reduces coronary spasm. In a clinical study in patients after myocardial infarction, verapamil reduced total mortality, sudden cardiac death and reinfarction rate.

Verapamil reduces total peripheral resistance and lowers high blood pressure by vasodilation, without reflex tachycardia. Because of its use-dependent action on the voltage-operated calcium channel, the effects of verapamil are more pronounced on high than on normal blood pressure.

As early as day one of treatment, blood pressure falls; the effect is found to persist also in long-term therapy. Verapamil is suitable for the treatment of all types of hypertension: for monotherapy in mild to moderate hypertension; combined with other antihypertensives (in particular with diuretics and, according to more recent findings, with ACE inhibitors) in more severe types of hypertension. In hypertensive diabetic patients with nephropathy, verapamil in combination with ACE inhibitors led to a marked reduction of albuminuria and to an improvement of creatinine clearance.

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. 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 SR verapamil is approximately 33%, owing to an extensive hepatic first-pass metabolism. Bioavailability is about two times higher with repeated administration. Peak verapamil plasma levels are reached four to five hours after SR administration. The peak plasma concentration of norverapamil is attained approximately five hours after SR administration. The presence of food has no effect on the bioavailability of verapamil.

Distribution

Verapamil is widely distributed throughout the body tissues, the volume of distribution ranging from 1.8–6.8 L/kg in healthy subjects. Plasma protein binding of verapamil is approximately 90%.

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

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.

5.3 Preclinical safety data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 0.6 (180 mg/m^2/day) and 1.2 times (360 mg/m^2/day) respectively the equivalent maximum recommended human oral daily dose (300mg/m^2/day) and have revealed no evidence of teratogenicity. In the rat, the highest dose was embryocidal and retarded foetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and weight gain of dams). This oral dose has also been shown to cause hypotension in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium alginate, microcrystalline cellulose, povidone, hypromellose, titanium dioxide (E171), silica colloidal anhydrous, magnesium stearate, macrogol 400, quinoline yellow aluminum lake (E104), indigo carmine aluminum lake (E132), carnauba wax.

6.2 Incompatibilities

None applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister.

Pack sizes: 10 and 30 caplets.

6.6 Special precautions for disposal and other handling

The caplets should be stored in the original blister, as the product is sensitive to moisture. In case of halving the caplet, discard half of the caplet that is not intended for immediate use.

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

7. MARKETING AUTORISATION HOLDER

Dexcel Ltd., 1 Dexcel Street, Or Akiva 3060000, Israel

8. MARKETING AUTHORISATION NUMBER

068-63-26427-00

Revised in July 2025 according to MOH guidelines