

## SUMMARY OF PRODUCT CHARACTERISTICS

### **Dilatam 120 SR Tablets Slow Release**

#### **1. NAME OF THE MEDICINAL PRODUCT**

Dilatam 120 SR

#### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 120 mg diltiazem hydrochloride.

For the full list of excipients, see section 6.1.

#### **3. PHARMACEUTICAL FORM**

Tablet slow release

White to off-white, round tablet, debossed "120" on one side and "D" on the other.

#### **4. CLINICAL PARTICULARS**

##### **4.1 Therapeutic indications**

Hypertension

either as monotherapy or with other antihypertensive medications such as diuretics.

Angina pectoris:

Chronic stable angina.

Angina due to coronary artery spasm.

##### **4.2 Posology and method of administration**

Note: Dilatam 120 SR Tablets are not suitable for use in patients who require less than 120 mg per dose, since the tablet is not divisible.

Hypertension

The usual recommended dosage of Dilatam 120 SR Tablets is one tablet twice daily. The dosage should be individualized and adjusted to the patient's needs.

The maximum antihypertensive effect is achieved usually by 14 days of chronic therapy. The usual optimum dosage range reported in clinical trials was 240-360 mg/day.

Angina Pectoris

The usual recommended dosage of Dilatam 120 SR Tablets is one tablet twice daily. The dosage should be individualized and adjusted to the patient's needs.

Concomitant Drug Therapy

An additive antihypertensive effect occurs when diltiazem is coadministered with other antihypertensives. Adjust the dose of Dilatam 120 SR or the concomitant antihypertensive accordingly.

Sublingual nitroglycerin may be taken as required to abort acute anginal attacks during Dilatam 120 SR therapy. Dilatam 120 SR may be also coadministered with prophylactic nitrate therapy.

### **4.3 Contraindications**

Hypersensitivity to diltiazem or to any of the excipients listed in section 6.1.

Pregnancy and in women of child bearing capacity.

Patients with severe bradycardia (less than 40 bpm), second or third degree heart block, sick sinus syndrome, decompensated cardiac failure, patients with left ventricular failure with pulmonary congestion.

Concurrent use with dantrolene infusion because of the risk of ventricular fibrillation (see section 4.5).

### **4.4 Special warnings and precautions for use**

The product should be used with caution in patients with reduced left ventricular function. Patients with mild bradycardia (risk of exacerbation), first degree AV block or prolonged PR interval should be observed closely.

Diltiazem is considered unsafe in patients with acute porphyria.

Prior to general anaesthesia, the anaesthetist must be informed of ongoing diltiazem treatment. Depression of cardiac contractility, conductivity and automaticity, as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

Increase of plasma concentrations of diltiazem may be observed in the elderly and in patients with renal or hepatic insufficiency. The contraindications and precautions should be carefully observed and close monitoring, particularly of heart rate, should be carried out at the beginning of treatment.

Calcium channel blocking agents, such as diltiazem, may be associated with mood changes, including depression.

Like other calcium channel antagonists, diltiazem has an inhibitory effect on intestinal motility. Therefore it should be used with caution in patients at risk to develop an intestinal obstruction. Tablet residues from slow release formulations of the product may pass into the patient's stools; however, this finding has no clinical relevance.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### **Concomitant use contraindicated:**

Dantrolene (infusion): Lethal ventricular fibrillation is regularly observed in animals when intravenous verapamil and dantrolene are administered concomitantly. The combination of a calcium antagonist and dantrolene is therefore potentially dangerous (see section 4.3).

#### **Concomitant use requiring caution:**

Lithium: Risk of increase in lithium-induced neurotoxicity.

Nitrate derivatives: Increased hypotensive effects and faintness (additive vasodilating effects): In all the patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out at gradually increasing doses.

Theophylline: Increase in circulating theophylline levels.

Alpha-antagonists: Increased antihypertensive effects: Concomitant treatment with alpha-antagonists may produce or aggravate hypotension. The combination of diltiazem with an alpha-antagonist should be considered only with the strict monitoring of the blood pressure.

Amiodarone, digoxin: Increased risk of bradycardia: Caution is required when these are combined with diltiazem, particularly in elderly subjects and when high doses are used. Diltiazem hydrochloride may cause small increases in plasma levels of digoxin, requiring careful monitoring of AV conduction.

Beta-blockers: Possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrioventricular conduction disturbances and heart failure (synergistic effect). Patients with pre-existing conduction defects should not receive the combination of diltiazem and beta-blockers. Such a combination must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.

Other antihypertensive drugs: Enhanced antihypertensive effect may occur with concomitant use of other antihypertensive drugs (e.g. beta-blockers, diuretics, ACE-inhibitors) or drugs that cause hypotension such as aldesleukin and antipsychotics.

Other antiarrhythmic agents: Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended (additive risk of increased cardiac adverse effects). This combination should only be used under close clinical and ECG monitoring.

Carbamazepine: Increase in circulating carbamazepine levels: It is recommended that the plasma carbamazepine concentrations be assayed and that the dose should be adjusted if necessary.

Rifampicin: Risk of decrease of diltiazem plasma levels after initiating therapy with rifampicin: The patient should be carefully monitored when initiating or discontinuing rifampicin treatment.

Anti-H<sub>2</sub> agents (cimetidine, ranitidine): Increase in plasma diltiazem concentrations. Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with anti-H<sub>2</sub> agents. An adjustment in diltiazem daily dose may be necessary.

Protease inhibitors (e.g. atazanavir, ritonavir): Increase in plasma diltiazem concentrations.

Cyclosporin: Increase in circulating cyclosporin levels: It is recommended that the cyclosporin dose be reduced, renal function be monitored, circulating cyclosporin levels be assayed and that the dose should be adjusted during combined therapy and after its discontinuation.

### **General information to be taken into account:**

Due to the potential for additive effects, caution and careful titration are necessary in patients receiving diltiazem concomitantly with other agents known to affect cardiac contractility and/or conduction.

Diltiazem is metabolized by CYP3A4. A moderate (less than 2-fold) increase of diltiazem plasma concentration in cases of co-administration with a stronger CYP3A4 inhibitor has been documented. Diltiazem is also a CYP3A4 isoform inhibitor. Co-administration with other CYP3A4 substrates may result in an increase in plasma concentration of either co-administered drug (e.g. , cilostazol, ivabradine, sirolimus, tacrolimus). Care should be exercised in patients taking these drugs. Concomitant use of diltiazem with cilostazol and ivabradine should be avoided.

Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

Barbiturates (phenobarbital, primidone): serum levels of diltiazem may be decreased by concomitant usage of CYP3A4 inducers.

Phenytoin: serum levels of diltiazem may be decreased by concomitant usage of CYP3A4 inducers. Diltiazem may increase serum levels of phenytoin.

Benzodiazepines (midazolam): Diltiazem significantly increases plasma concentrations of midazolam and prolongs its half-life. Special care should be taken when prescribing short-acting benzodiazepines metabolized by the CYP3A4 pathway in patients using diltiazem.

Diltiazem may increase bioavailability of tricyclic antidepressants.

Corticosteroids (methylprednisolone): Inhibition of methylprednisolone metabolism (CYP3A4) and inhibition of P-glycoprotein: The patient should be monitored when initiating methylprednisolone treatment. An adjustment in the dose of methylprednisolone may be necessary.

Statins (simvastatin, atorvastatin): Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis due to statins metabolised by CYP3A4 may be increased with concomitant use of diltiazem. When possible, a non CYP3A4-metabolised statin should be used together with diltiazem, otherwise close monitoring for signs and symptoms of a potential statin toxicity is required.

Dilatam 120 SR tablets should not be taken at the same time as alcohol, as it may increase the rate of release of diltiazem from the prolonged release preparation. In addition the combination of alcohol and diltiazem may have an additive vasodilatory effect.

#### **4.6 Fertility, pregnancy and lactation**

##### **Pregnancy**

There is very limited data from the use of diltiazem in pregnant patients. Diltiazem has been shown to have reproductive toxicity in certain animal species (rat, mice, rabbit). Diltiazem is contraindicated during pregnancy (see section 4.3), as well as in women of child-bearing potential not using effective contraception.

##### **Breast-feeding**

Diltiazem is excreted in breast milk at low concentrations. Breast-feeding while taking this drug should be avoided. If use of diltiazem is considered medically essential, an alternative method of infant feeding should be instituted.

#### **4.7 Effects on ability to drive and use machines**

Diltiazem has been reported to cause adverse reactions such as dizziness (common) and malaise (common), which may impair patients' ability to drive or operate machinery to a varying extent depending on the dosage and individual susceptibility. However, no studies have been performed. Therefore, patients should not drive or operate machinery if affected.

#### **4.8 Undesirable effects**

The following frequencies are the basis for assessing undesirable effects:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

	<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Not known</b>
<i>Blood and lymphatic system disorders</i>					Thrombocytopenia
<i>Immune system disorders</i>			Hypersensitivity		
<i>Psychiatric disorders</i>			Nervousness, insomnia		Mood changes (including depression)
<i>Nervous system disorders</i>		Headache, dizziness			Extrapyramidal syndrome
<i>Cardiac disorders</i>		Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations	Bradycardia		Sinoatrial block, congestive heart failure
<i>Vascular disorders</i>		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis), hypotension
<i>Gastrointestinal disorders</i>		Constipation, dyspepsia, gastric pain, nausea	Vomiting, diarrhoea	Dry mouth	Gingival hyperplasia
<i>Hepatobiliary disorders</i>			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis
<i>Skin and subcutaneous tissue disorders</i>		Erythema, pruritus		Urticaria	Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), hyperhidrosis,

					exfoliative dermatitis, acute generalized exanthematous pustulosis, desquamative erythema with or without fever, allergic dermatitis.
<i>Reproductive system and breast disorders</i>					Gynaecomastia
<i>General disorders and administration site conditions</i>	Peripheral oedema	Malaise, fatigue			

#### 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 clinical effects of acute overdose can involve pronounced hypotension possibly leading to collapse, sinus bradycardia with or without isorhythmic dissociation and atrioventricular conduction disturbances.

Treatment in a hospital setting will include gastric lavage and/or osmotic diuresis.

Conduction disturbances may be managed by temporary cardiac pacing.

Proposed corrective treatments: atropine, vasopressors, inotropic agents, glucagon and calcium gluconate infusion.

Symptomatic bradycardia and high grade atrioventricular block may respond to atropine and isoprenaline.

The formulation employs a prolonged release system which will continue to release diltiazem for some hours.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Selective calcium channel blocker with direct cardiac effects

ATC Code: C08D B01

Diltiazem is an antianginal agent and calcium antagonist. Diltiazem inhibits transmembrane calcium entry in myocardial muscle fibres and in vascular smooth muscle fibres, thereby decreasing the quantity of intracellular calcium available to the contractile proteins.

#### **5.2 Pharmacokinetic properties**

Dilatam 120 SR Tablets is a form characterised by prolonged release of diltiazem hydrochloride in the digestive tract.

Diltiazem is 80% bound to human plasma proteins (albumin, acid glucoproteins).

The biotransformation routes are:

- Deacetylation
- Oxidative o- and n-demethylation
- Conjugation of the phenolic metabolites.

The primary metabolites, n-demethyldiltiazem and desacetyldiltiazem exert less pharmacological activity than diltiazem. The other metabolites are pharmacologically inactive.

After administration of 180 to 300 mg of Diltiazem SR capsules, a peak plasma concentration of 80 to 220 ng/ml, respectively, is obtained after about 5.5 hours.

The elimination half-life varies from 6 to 8 hours, depending on the strength.

### **5.3 Preclinical safety data**

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Hydroxypropyl methyl cellulose, povidone, hydroxypropyl cellulose, talc, polyethylene glycol 6000, colloidal silicon dioxide, hydrogenated vegetable oil, magnesium stearate, polyethylene glycol 4000.

### **6.2 Incompatibilities**

None known.

### **6.3 Shelf life**

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

### **6.4 Special precautions for storage**

Store in a dry and dark place below 25°C.

### **6.5 Nature and contents of container**

PVC/Aluminium blister packages.

Each package contains 10, 30 or 60 tablets.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

Not applicable

## **7. LICENCE HOLDER AND MANUFACTURER**

TEVA ISRAEL LTD

124 Dvora HaNevi'a St., Tel Aviv 6944020 Israel

## **8. REGISTRATION NUMBER**

057.29.26825

The leaflet was revised in December 2021 according to MOHs guidelines.