# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Mezatil SR 120mg Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 120mg Diltiazem hydrochloride.

Excipients with known effect: Each capsule contains 50mg sucrose

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard capsule

Opaque pink and orange capsule containing diltiazem hydrochloride in sustained release sugar beads.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

*Posology*
**Adult**

For all indications the usual initial dose is 90mg twice daily. Depending on clinical response, the patient's dosage may be increased to 180mg twice daily if required.

**Elderly and patients with impaired hepatic or renal function**
Dosage should commence at the lower level of 60mg twice daily and be increased slowly in order to achieve the required level of control. The daily dose should not exceed 90mg twice daily. Do not increase the dose if the heart rate falls below 50 beats per minute.

**Paediatric population**
Not recommended.

*Method of administration*
The method of administration is by oral use. To be swallowed whole, not chewed.

## 4.3 Contraindications

- Hypersensitivity to diltiazem or any of the excipients
- Pregnancy, Lactation ( see section 4.6 )
- In women of child bearing potential who are not using effective contraception. (see section 4.6).
- In patients with severe bradycardia (less than 40 beats per minute), second or third degree heart block or sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- In patients with cardiac failure after myocardial infarction; left ventricular failure with stasis or with pulmonary congestion.
- Severe aortic stenosis
- Cardiogenic shock
- Severe hypotension (systolic blood pressure less than 90mmHg)
- Concomitant administration of dantrolene infusion. (see section 4.5).
- Acute porphyria unless a safe alternative is not available
- Concurrent use with lomitapide (see section 4.5)
- Combination with ivabradine (see section 4.5).

Additionally, for the intravenous forms, patients known to have an accessory bypass (Wolf-Parkinson-White syndrome or short PR syndrome), and who develop atrial fibrillation or flutter, should not be administered intravenous diltiazem.

## 4.4 Special warnings and precautions for use

Rare instances of hyperglycaemia have been reported in association with diltiazem hydrochloride. The use of diltiazem hydrochloride in diabetic patients may require adjustment of their control.

The product should be used with caution in patients with hepatic dysfunction or with impaired renal function.

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.

Abnormalities of liver function have been received, these reactions have been reversible upon discontinuation of therapy.

Closed observation is necessary in patients with reduced left ventricular function. bradycardia (risk of exacerbation) or with, 1$^{st}$ degree atrio-ventricular block or prolonged PR interval detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).

Cases of acute renal failure secondary to decreased renal perfusion have been reported in patients with existing cardiac disease especially reduced left ventricular function, severe bradycardia or severe hypotension. Careful monitoring of renal function is advised.

Prior to general anaesthesia, the anaesthesist 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.

Do not suck or chew capsules.

Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

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.

Capsule 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).

There is a risk of arrhythmias when diltiazem is given with intravenous dantrolene.

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

*Lomitapide:*
Diltiazem (a moderate CYP3A4 inhibitor) may increase lomitadpide plasma concentrations through CYP3A4 inhibition leading to increased risk of elevations in liver enzymes (see section 4.3).

**Concomitant use requiring caution:**

*Antihypertensives:*
Diltiazem hydrochloride should be administered with great care to patients receiving concurrent treatment with antihypertensives or other hypotensive agents including halogenated anaesthetics or drugs with moderate protein binding.

Patients receiving, diuretics, ACE inhibitors or other antihypertensive agents should be regularly monitored.

*Alpha-antagonists:*
Increased antihypertensive effects: Concomitant treatment with alphaantagonists 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.

*Beta-blockers:*
Possibility of rhythm disturbances (pronounced bradycardia, sinus arrest), sino-atrial and atrio-ventricular conduction disturbances and heart failure (synergistic effect). Such a combination must only be used under close clinical and ECG monitoring, particularly at the beginning of treatment.

Diltiazem hydrochloride will not protect against effects of withdrawal of betaadrenoceptor blocking agents, nor the rebound effects seen with various antihypertensives. Combination with beta-adrenoceptor blockers having significant 'first pass' loss, e.g. propanolol, may require a decrease in their dose and may lead to bradycardia.

The blood levels of beta blockers with a low bioavailability (*eg* propranolol) may be increased and small increases in the plasma levels of digitalis glycosides have been observed.

Intravenous administration of beta blockers should be discontinued during therapy with diltiazem.

*Antiarrhythmics:*
The simultaneous administration of beta blockers, antiarrhythmics or heart glycosides may cause a greater degree of AV blocking, reduce the heart rate or induce a hypotensive effect.

*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).

There may be an additive effect when used with drugs which may induce bradycardia or with other antihypertensives, or other antiarrhythmic drugs This combination of drugs must be subjected to the highest caution and should only be used under close clinical and ECG monitoring.

*Digoxin:*
Diltiazem hydrochloride may increase the blood levels of concomitant digoxin.

Increased risk of bradycardia: Caution is required when this is combined with diltiazem, particularly in elderly subjects and when high doses are used.

*Antiepileptics:*
Diltiazem increases plasma concentrations of phenytoin. The effects of diltiazem are reduced by phenobarbital and phenytoin. The effects of diltiazem are probably reduced by primidone.

*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.

*Anti-retroviral drugs:*
Efavirenz reduces the plasma concentration of diltiazem.
The antiviral drug atazanivir increases the plasma concentration of diltiazem. Amprenavir and ritonavir possibly increase the plasma concentration of diltiazem.

*Anaesthetics:*
Diltiazem hydrochloride has been continued in anaesthesia without problems, but the anaesthetist should be made aware that the patient is taking this medication because of the potential for synergism or interactions with other agents used in anaesthesia. Diltiazem inhibits the metabolism of alfentanil, with the risk of prolonged or delayed respiratory depression. The depression of cardiac contractility, conductivity and automaticity as well as vascular dilation associated with anaesthetics may be potentiated by calcium blockers. The plasma concentration of both drugs may increase when diltiazem is given with nifedipine.

*Warfarin, Rifampicin:*
There have been reports in the literature of diltiazem interactions with warfarin, rifampicin,

*Lithium:*
Risk of increase in lithium-induced neurotoxicity.
There have been reports in the literature of diltiazem interaction with lithium.

*Nitrate derivatives:*

Increased hypotensive effects and faintness (additive vasodilatating 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

*Amiodarone:*
Amiodarone-induced risk of bradycardia, AV block and myocardial depression is increased by diltiazem.

Increased risk of bradycardia. Caution is required when this is combined with diltiazem, particularly in elderly subjects and when high doses are used.

*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.

*$H_2$ antagonists* (cimetidine, ranitidine):
Increase in plasma diltiazem concentrations.
Patients currently receiving diltiazem therapy should be carefully monitored when initiating or discontinuing therapy with anti-$H_2$ agents. An adjustment in diltiazem daily dose may be necessary.

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

Diltiazem increases plasma concentrations of tacrolimus and sirolimus, and buspirone, cilostazol, ivabradine, dutasteride, imipramine, eplerenone and atorvastatin.

Concomitant use of diltiazem with cilostazol should be avoided.

**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 undergoes biotransformation by cytochrome P-450 mixed function oxidase (CYP3A4). Co-administration with other agents which follow the same route of biotransformation may result in competitive inhibition of metabolism.
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. Co-administration of diltiazem with a CYP3A4 inducer may result in a decrease of diltiazem plasma concentrations.

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

*Statins:*
When diltiazem is given with simvastatin there is a possible increased risk of myopathy.

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.

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

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
There is very limited data from the use of diltiazem in pregnant patients.
Diltiazem must not be used at any time during pregnancy as well as in women of child-bearing potential who are not using effective contraception as it is teratogenic in some animal species (rat, mice, rabbit). There is no experience of its effects in humans.

*Breast-feeding*
Diltiazem must not be given during lactation. Diltiazem is known to readily enter the breast milk at low concentrations and there is no experience of possible effect in infants, 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

On the basis of reported adverse drug reactions, i.e. dizziness (common), malaise (common), the ability to drive and use machines could be altered. However, no studies have been performed.

## 4.8 Undesirable effects

*The following CIOMS frequency rating is used, when applicable: 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).*

Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

| | **Very common** | **Common** | **Uncommon** | **Rare** | **Not known** |
|---|---|---|---|---|---|
| *Blood and lymphatic system disorders* | | | | | Thrombocytopenia, lymphadenopathy, Eosinophilia |
| *Psychiatric disorders* | | | Nervousness, insomnia | | Mood changes (including depression), hallucination, personality change, |
| *Nervous system disorders* | | Headache, dizziness | | | Extrapyramidal syndrome, syncope, amnesia, paraesthesia, somnolence, tremor |

| | **Very common** | **Common** | **Uncommon** | **Rare** | **Not known** |
|---|---|---|---|---|---|
| *Cardiac disorders* | | Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations | Bradycardia | | Sinoatrial block, congestive heart failure, angina, arrhythmia, congestive heart failure, palpitations |
| *Vascular disorders* | | Flushing | Orthostatic hypotension | | Vasculitis (including leukocytoclastic vasculitis), hypotension |
| *Gastrointestinal disorders* | | Constipation, dyspepsia, gastric pain, nausea | Vomiting, diarrhea | Dry mouth | Gingival hyperplasia, anorexia, gingivitis, gingival hypertrophy |
| *Hepatobiliary disorders* | | | Hepatic enzymes increase (AST, ALT, LDH, ALP increase) | | Hepatitis |
| *Skin and subcutaneous tissue disorders* | | Erythema | | Urticaria | Photosensitivity (including lichenoid keratosis at sun exposed skin areas), angioneurotic oedema, rash, erythema multiforme (including Steven-Johnson's syndrome and toxic epidermal necrolysis), sweating, exfoliative dermatitis, acute generalized exanthematous pustulosis, occasionally desquamative erythema with or without fever, petechiae, pruritus, Lupus-like syndrome. |

| | **Very common** | **Common** | **Uncommon** | **Rare** | **Not known** |
|---|---|---|---|---|---|
| *Reproductive system and breast disorders* | | | | | Gynecomastia, sexual dysfunction |
| *General disorders and administration site conditions* | Peripheral oedema | Malaise | | | Gait abnormality |
| *Investigations* | | | | | Weight increase, CK elevation, |
| *Eye disorder* | | | | | Amblyopia |
| *Ear and labyrinth disorders* | | | | | Tinnitus |
| *Respiratory, thoracic and mediastinal disorders* | | | | | Dyspnoea, epistaxis, nasal congestion |
| *Metabolism and nutrition disorders* | | | | | Hyperglycemia |
| *Renal and urinary disorders* | | | | | Nocturia, polyuria |
| *Musculoskeletal and connective tissue disorders* | | | | | Osteoarticular pain, muscle pain |

In studies carried out to date, serious adverse reactions with diltiazem have been rare; however, it should be recognised that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

In 900 patients with hypertension, the most common adverse events were oedema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first degree AV block (3%). Only oedema and perhaps bradycardia were dose related. The most common adverse events (>1%) observed in clinical studies of over 2100 angina and hypertensive patients receiving diltiazem were: oedema

(5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%) and rash (1.5%).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

## 4.9 Overdose

The clinical effects of acute overdose can involve pronounced hypotension leading to collapse and acute kidney injury, sinus bradycardia with or without isorhythmic dissociation, sinus arrest, atrioventricular conduction disturbances and cardiac arrest.
Experience of overdosage in man is limited, but cases of spontaneous recovery have been reported. However, it is recommended that patients with suspected overdose, should be placed under observation in a coronary care unit with facilities available for treatment of any possible hypotension and conduction disturbances that may occur.

Most patients suffering from overdosage of diltiazem become hypotensive within 8 hours of ingestion. With bradycardia and first to third degree atrioventricular block also developing, cardiac arrest may ensue.
Hyperglycaemia is also a recognised complication. The elimination half-life of diltiazem after overdosage is estimated to be about 5.5-10.2 hours. If a patient presents early after overdose, treatment, in a hospital setting, will include gastric lavage should be performed and activated charcoal administered to reduce diltiazem absorptionand/or to be treated with osmotic diuresis.

Hypotension should be corrected with plasma expanders, intravenous calcium gluconate infusion, vasopressors, glucagon and inotropic agents (dopamine, dobutamine or isoprenaline). Symptomatic bradycardia and high grade AV block may respond to atropine, isoprenaline or occasionally cardiac pacing which may be useful if conduction disturbances and/or cardiac standstill occurs.

Mezatil Capsules SR are extended release capsules and effects may be slow in onset and prolonged, therefore monitoring

should be carried out for longer periods than following overdose with immediate release dosage forms.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Calcium antagonist, antianginal and antihypertensive agent.

Pharmacotherapeutic group: Calcium Channel Blocker, ATC Code: C08D B01

Mechanism of action
Diltiazem has pharmacological actions similar to those of other calcium channel blocking agenst such as nifedipine or verapamil. The principal physiological action of diltiazem is to inhibit the transmembrane influx of extracellular calcium ions across the membranes of myocardial cells and in vascular smooth cells.

Calcium plays important roles in the excitation-contraction coupling processes of the heart and vascular smooth muscle cells and in the electrical discharge of the specialised conduction cells of the heart. The membranes of these cells contain numerous channels that carry a slow inward current that are selective for calcium.

By inhibiting calcium influx, diltiazem inhibits the contractile processes of cardiac and vascular smooth muscle, thereby dilating the main coronary and systemic arteries. Dilation of systemic blood pressure and a decrease in total peripheral resistance, a decrease in systemic blood pressure and a decrease in the afterload of the heart. The reduction in afterload, seen at rest and with exercise and its resultant decrease in myocardial oxygen consumption, are thought to be responsible for the beneficial effects of diltiazem in patients with chronic stable angina pectoris. In patients with Prinzmetal's variant angina, inhibition of spontaneous and ergometrine-induced coronary artery spasm by diltiazem results in increased myocardial oxygen delivery.

## 5.2 Pharmacokinetic properties

Absorption
Diltiazem is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration, but undergoes extensive first-pass hepatic metabolism.

Distribution
The bioavailability has been reported to be about 40%, although there is considerable inter-individual variation in plasma concentrations.

Diltiazem is about 80% bound to plasma proteins.

Biotransformation
Diltiazem is extensively metabolised in the liver; one of the metabolites, desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound.

Elimination
The half-life is reported to be about 3 to 4 hours. Approximately 60% of the dose is excreted in the bile and 35 to 40% in the urine, and 2 to 4% as unchanged diltiazem.

### 5.3 Preclinical safety data

Not applicable.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sugar spheres (75% sucrose; 25% corn starch)
Povidone
Methacrylic acid copolymer
Ethylcellulose
Diethyl phthalate
Talc
Hard gelatin capsules containing E 171 (Titanium dioxide), E 172 (Red iron oxide, Yellow iron oxide),

### 6.2 Incompatibilities

No known incompatibilities.

### 6.3 Shelf life

The shelf-life of the product, as packaged for sale, is 4 years.

There are no data available on the shelf-life of the product after first opening the container.

### 6.4 Special precautions for storage

Do not store above 25° C.

### 6.5 Nature and contents of container

- PVC/aluminium foil blister strips in packs of 14, 28, 42, 56 and 84 capsules.
- High density, white polyethylene ‘tablet containers’ with white polypropylene screw caps containing 100 capsules.

Both containers are enclosed in outer cardboard cartons, which also contain a patient information leaflet.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

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

## 7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited

11 Boumpoulinas

Nicosia

1060

Cyprus

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0206

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 Dec 2001

## 10 DATE OF REVISION OF THE TEXT

07/08/2023