SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Angitil SR 90 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Angitil SR 90 mg Capsules
Each capsule contains 90 mg of Diltiazem Hydrochloride

Excipients with known effect:
Each 90 mg capsule contains:
Sucrose (21.38 mg/capsule)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release capsule, hard.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the management of angina pectoris. For the management of mild to moderate hypertension.

4.2 Posology and method of administration

Posology:
Individual patients' responses to diltiazem may vary, necessitating careful titration.

Angitil SR 90 mg, 120 mg and 180 mg Capsules are taken twice daily. Angitil XL 240 mg and 300 mg Capsules are taken once daily.

Adults:

The usual initial dose is 90 mg twice daily. Dosage may be increased gradually to 120 mg twice daily or 180 mg twice daily if required.

Patients currently receiving a total daily dose of 180 mg diltiazem (as 90 mg *bd*), may be titrated up to 240 mg (*od*). A patient receiving 240 mg per day of diltiazem (as 120 mg *bd*), should commence treatment on the 240 mg capsule (*od*), titrating to the 300 mg capsule (*od*), if required.

Elderly and patients with impaired renal or hepatic dysfunction:

The starting dose should be 60 mg diltiazem twice daily. If necessary, the dose may be increased gradually but careful monitoring of this group of patients is advised. Where the patient is currently prescribed 120 mg this dose may, by careful titration, be increased to 240 mg *(od).*

Paediatric population:

Diltiazem preparations are not recommended for children. Safety and efficacy in children have not been established.

In order to avoid confusion, it is suggested that patients once titrated to an effective dose should remain on this treatment and should not be changed between different presentations.

Method of administration

Route of administration: Oral

The capsules should be swallowed whole and not chewed. Dosage may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to diltiazem or to any of the excipients listed in section 6.1.
- Sick sinus syndrome, 2nd or 3rd degree AV block in patients without a functioning pacemaker.
- Severe bradycardia (less than 50 beats per minute).
- Left ventricular failure with pulmonary stasis.
- Decompensated cardiac failure.
- Lactation.

- Concurrent use with dantrolene infusion (see section 4.5).
- Combination with ivabradine (see section 4.5).
- Concurrent use with lomitapide (see section 4.5).
- Concurrent use with asunaprevir (see section 4.5).

4.4 Special warnings and precautions for use

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) or with a 1st degree AV 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.

Increase of plasma concentrations of diltiazem may be observed in the elderly and 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.

In the case of general anaesthesia, the anaesthetist must be informed that the patient is taking diltiazem. The depression of cardiac contractility, conductivity and automaticity as well as the vascular dilatation associated with anaesthetics may be potentiated by calcium channel blockers.

Treatment with diltiazem may be associated with mood changes, including depression (see section 4.5 and 4.8). Early recognition of relevant symptoms is important, especially in predisposed patients. In such cases, drug discontinuation should be considered.

Diltiazem has an inhibitory effect on intestinal motility. Therefore, it should be used with caution in patients at risk of developing an intestinal obstruction.

Careful monitoring is necessary in patients with latent or manifest diabetes mellitus due to a possible increase in blood glucose.

The use of diltiazem may induce bronchospasm, including asthma aggravation, especially in patients with preexisting bronchial hyper-reactivity. Cases have also been reported after dose increase. Patients should be monitored for signs and symptoms of respiratory impairment during diltiazem therapy.

Diltiazem in considered unsafe in patients with acute porphyria.

Residues from slow-release formulations of the product may pass into the patient's stools; however, this finding has no clinical relevance.

Caution should be exercised when direct oral anticoagulants (DOACs) are co-administered with Diltiazem which is a moderate CYP3A4 and a weak P-gp inhibitor, particularly in patients at high risk of bleeding (see section 4.5).

This medicine contains less than 1 mmol sodium (23mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Combination Contraindicated For Safety Reasons:

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).

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 lomitapide plasma concentrations through CYP3A4 inhibition leading to increased risk of elevations in liver enzymes (see section 4.3).

Asunaprevir

Diltiazem (a moderate CYP3A4 inhibitor) may increase asunaprevir plasma concentrations through CYP3A4 inhibition (see section 4.3).

Combinations Requiring Caution:

Alpha-antagonists

Increased anti-hypertensive effects. Concomitant treatment with alpha-antagonists may produce or aggravate hypotension. The combination of diltiazem with an alpha antagonist should be considered only with strict monitoring of 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.

An increased risk of depression has been reported when diltiazem is co-administered with beta-blockers (see section 4.8).

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.

Antiarrhythmic agents

Since diltiazem has antiarrhythmic properties, its concomitant prescription with other antiarrhythmic agents is not recommended due to the risk of increased cardiac adverse effects due to an additive effect. This combination should only be used under close clinical and ECG monitoring.

Nitrate derivatives

Increased hypotensive effects and faintness (additive vasodilating effects).

In all patients treated with calcium antagonists, the prescription of nitrate derivatives should only be carried out at gradually increasing doses.

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.

Phenytoin

When co-administered with phenytoin, diltiazem may increase phenytoin plasma concentration.

It is recommended that the phenytoin plasma concentrations be monitored.

X-Ray Contrast Media

Cardiovascular effects of an intravenous bolus of an ionic X-ray contrast media, such as hypotension, may be increased in patients treated with diltiazem.

Special caution is required in patients who concomitantly receive diltiazem and X-ray contrast media.

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.

Theophylline

Increase in circulating theophylline levels.

Anti-H_2 agents (cimetidine and 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.

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.

Lithium

Risk of increase in lithium-induced neurotoxicity.

Antiplatelet drugs

In a pharmacodynamic study, diltiazem was shown to inhibit platelet aggregation. Although the clinical significance of this finding is unknown, potential additive effects when used with antiplatelet drugs should be considered.

Combinations To Be Taken Into Account:

Diltiazem is metabolised 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.

Grapefruit juice may increase diltiazem exposure (1.2 fold). Patients who consume grapefruit juice should be monitored for increased adverse effects of diltiazem. Grapefruit juice should be avoided if an interaction is suspected.
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.

Statins

Diltiazem is an inhibitor of CYP3A4 and has been shown to significantly increase the AUC of some statins. The risk of myopathy and rhabdomyolysis is increased by concomitant administration of diltiazem with statins metabolised by CYP3A4 (e.g. atorvastatin, fluvastatin, and simvastatin). An adjustment of the dose of statin may be necessary (see also product information of the relevant statin). When possible, it is recommended to use a

statin not metabolised by CYP3A4 (e.g. pravastatin) with diltiazem. Otherwise, close monitoring for signs and symptoms of potential statin toxicity is required.

Cilostazol

Inhibition of cilostazol metabolism (CYP3A4). Diltiazem has been shown to increase cilostazol exposure and to enhance its pharmacological activity.

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 metabolised by the CYP3A4 pathway in patients using diltiazem.

Corticosteroids (methylprednisolone)

Diltiazem can increase methylprednisolone levels (through inhibition of CYP3A4 and possible inhibition of P-glycoprotein). The patient should be monitored when initiating methylprednisolone treatment. An adjustment to the dose of methylprednisolone may be necessary.

Colchicine

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

Diltiazem which is a moderate CYP3A4 and weak P-gp inhibitor may increase the plasma concentration of DOACs when co-administered with Diltiazem.

Diltiazem may lead to QT prolongation, when administered with drugs with potential/ known for prolonging the QT interval. Co-administration of diltiazem with drugs known to prolong the QT interval must be based on a careful assessment of the potential risks and benefits of the treatment.

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.

Angitil capsules should not be taken at the same time as alcohol. In vitro data suggests that in combination with Angitil capsules, alcohol may increase the rate of in vivo release of the product from the prolonged-release preparation. Alcohol may increase dose-dependent effects and lead to potential adverse pharmacodynamic interactions. Alcohol use could therefore increase the rate and seriousness of diltiazem adverse drug reactions such as vasodilatory related events.

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 (see section 5.3) in certain animal species (rat, mice, rabbit). Diltiazem is therefore not recommended during pregnancy, as well as in women of child-bearing potential not using effective contraception.

Breast feeding

As this drug is excreted in breast milk, breast feeding whilst taking diltiazem is contraindicated.

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
Psychiatric disorders			Nervousness, insomnia		Mood changes including depression
Nervous system disorders		Headache, dizziness			Extrapyramidal syndrome
Respiratory, thoracic and mediastinal disorders					Bronchospasm (including asthma aggravation)
Cardiac disorders		Atrioventricular block (may be of first, second or third degree; bundle branch block may occur), palpitations	Bradycardia		Sinoatrial block, congestive heart failure sinus arrest, cardiac arrest (asystole)
Vascular disorders		Flushing	Orthostatic hypotension		Vasculitis (including leukocytoclastic vasculitis)
Gastro-intestinal disorders		Constipation, dyspepsia, gastric pain, nausea	Vomiting, diarrhoea	Dry mouth	Gingival hyperplasia
Metabolism and nutrition disorders					Hyperglycemia

Hepato-biliary disorders			Hepatic enzymes increase (AST, ALT, LDH, ALP increase)		Hepatitis
Skin and sub-cutaneous 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, lupus-like syndrome, lichenoid drug eruption
Reproductive system and breast disorders					Gynecomastia
General disorders and administration site conditions	Peripheral oedema	Malaise			

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of diltiazem overdose that may manifest with a delay onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment, under hospital supervision, will include gastric lavage, osmotic diuresis. Conduction disturbances may be managed by temporary cardiac pacing.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers; Benzothiazepine derivatives, ATC code: C08DB01

Diltiazem is an antianginal agent, calcium antagonist, antihypertensive agent.

Diltiazem restricts calcium entry into the slow calcium channel of vascular smooth muscle and myocardial muscle fibres in a voltage-dependent manner. By this mechanism, diltiazem reduces the concentration of intracellular calcium in contractile protein.

In animals: diltiazem increases coronary blood flow without inducing any coronary steal phenomena. It acts both on small, large and collateral arteries. This vasodilator effect, which is moderate on peripheral systemic arterial territories, can be seen at doses that are not negatively inotropic.

The two major active circulating metabolites, i.e. desacetyl diltiazem and N-monodesmethyl diltiazem, possess pharmacological activity in angina corresponding to 10 and 20% respectively of that of the parent compound.

In humans: diltiazem increases coronary blood flow by reducing coronary resistance.

Due to its moderate bradycardia-inducing activity and the reduction in systemic arterial resistance, diltiazem reduces cardiac workload.

Angitil Capsules does not have a significant myocardial depressant action in man.

5.2 Pharmacokinetic properties

Angitil capsules contain slow release forms of microgranules which permit diltiazem hydrochloride to be released along a length of the gastrointestinal 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 180mg to 300mg of the diltiazem formulation, a peak plasma concentration of 80ng/ml to 220 ng/ml, respectively, is obtained after 5.5 hours.

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

5.3 Preclinical safety data

Pregnancy: Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from 4 to 6 times (depending on species) the upper limit of the optimum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60-kg patient) resulted in embryo and fetal lethality. These studies revealed, in one species or another, a propensity to cause fetal abnormalities of the skeleton, heart, retina, and tongue. Also observed were reductions in early individual pup weights, pup survival, as well as prolonged delivery times and an increased incidence of stillbirths.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Sugar spheres (containing sucrose and maize starch)
Povidone K30
Sucrose
Ethylcellulose
Purified Talc
Dibutyl sebacate
Sodium Lauryl Sulfate
Cetyl Alcohol

Capsule Shell:
Gelatin
Titanium dioxide (E171)

Black Ink:
Shellac, propylene glycol, ammonium hydroxide, potassium hydroxide, E172 black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

The capsules should be stored in their original packaging. Do not store above 30°C.

6.5 Nature and contents of container

Capsules are enclosed in 250µm PVC/ 20µm aluminium blisters which are boxed in cardboard cartons containing 28 or 56 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ethypharm
194, Bureaux de la Colline – Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

Angitil SR 90 mg Capsules: PL 06934/0195

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/02/2005

10 DATE OF REVISION OF THE TEXT

22/07/2025