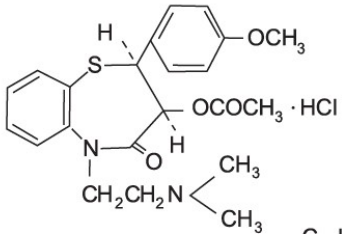
Ca^{++} -Antagonist

HERBESSER® 90 SR

(COMPOSITION AND DESCRIPTION)

Physicochemical properties of active ingredient

- INN (name in J.P.): Diltiazem hydrochloride
- Chemical name: (2S,3S)-5-[2-(Dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl-acetate monohydrochloride



$C_{22}H_{26}N_2O_4S.HCl$: 450.98

- Description:
- Diltiazem hydrochloride occurs as white crystals or crystalline powder. It is odorless.
- It is very soluble in formic acid, freely soluble in water, in methanol and in chloroform, sparingly soluble in acetonitrile, slightly soluble in dehydrated ethanol and in acetic anhydride, and practically insoluble in ether.
- Melting point: 210° - 215° C (decomposition)

Product's name	Content of Diltiazem hydrochloride	Description of the product
HERBESSER 90 SR	90 mg per capsule	white sustained - release capsule

(ACTIONS)

(PHARMACOLOGICAL STUDIES)

The therapeutic benefits achieved with HERBESSER 90 SR such as improvement of myocardial ischemia and hypotensive effect are believed to be related to its ability to dilate vessels by inhibiting the influx of calcium ion into coronary and peripheral vessels of smooth muscle cell.

1. Action on blood pressure
(1) Lowers the elevated blood pressure gradually although hardly affects the normal blood pressure (rat, human).
Suppresses the elevation of blood pressure induced by exercise load (human).
(2) Lowers blood pressure without decreasing cerebral and renal blood flow (dog, human).
(3) Suppresses myocardial and vascular hypertrophy together with lowering blood pressure (rat).

2. Effects on myocardial ischemia
(1) Increases coronary blood flow into myocardial ischemic region by dilating the collateral channels

and large coronary artery (dog).
(2) Suppresses coronary artery spasms (monkey, human).
(3) Decreases myocardial oxygen consumption without decreasing cardiac output by decreasing after-load and heart rate due to peripheral vasodilating effect (dog).
(4) Retains cardiac function and myocardial energy metabolism and reduces the infarct size by inhibiting extra calcium ion influx during myocardial ischemia (rat).

3. Action on sinus rhythm and cardiac conduction system
Slightly prolongs spontaneous sinus rhythm interval and A-V node conduction time. Does not affect on His-Purkinje conduction time (dog, human).

(PHARMACOKINETICS)

1. Plasma level
When 1 capsule (90 mg as diltiazem hydrochloride) of HERBESSER 90 SR was orally administered to healthy adult men, its plasma level reached the peak (about 40 ng/ml) about 7 hours after administration.
The plasma elimination half life was about 8.4 hours. In case of repeated administration of HERBESSER 90 SR twice a day to healthy adult men, plasma level at 1 to 10 hours after administration was about 91 ng / ml.

2. Metabolism
When HERBESSER 90 SR was administered to healthy adult men, deacetyl diltiazem, deacetyl-N-monodemethyl diltiazem, deacetyl-O-demethyl diltiazem, deacetyl-N,O-demethyl diltiazem and N-monodemethyl diltiazem were detected in urine as metabolites. A part of these metabolites are conjugated with glucuronic acid or sulfuric acid in body.

(CLINICAL STUDIES)

1. Hypertension
Usefulness of HERBESSER 90 SR in the treatment of essential hypertension was proved by four double-blind comparative studies with placebo, reserpine and propranolol as control drugs.

2. Angina pectoris
Usefulness of HERBESSER 90 SR in the treatment of anginal pain due to effort angina and old myocardial infarction was proved by two double-blind comparative studies including a placebo-controlled study.

3. Adverse reactions
432 cases (4.5%) of adverse reactions were reported out of total 9,347 cases. The most common occurrences as well as their frequency of presentation are Gastrointestinal system 1.3% (stomach discomfort 0.2%, constipation 0.2%, abdominal pain 0.1%, etc), cardiovascular system 1.3% (bradycardia 0.4%, dizziness 0.4%, hot flush of face 0.2%, A-V block 0.2%, etc.) hypersensitivity 1.2%, headache 0.2%, etc.

(PRECLINICAL STUDIES)

1. Toxicity

(1) Acute toxicity (LD_{50} mg/kg)

Route / Animal / Sex	p.o.		s.c.		i.v.	
	♂	♀	♂	♀	♂	♀
ddY - strain mouse	740	640	260	280	61	58
Wistar - strain rat	560	610	520	550	38	39

(2) Chronic toxicity
When 2, 10 and 25 mg/kg/day each of diltiazem hydrochloride were given orally to SD - strain rats and 5, 10 and 20 mg/kg/day to beagle dogs, for successive six months respectively, general state as well as urinary and histopathological findings of these animals were not significantly different from those of the control. Hematological findings in dogs given orally 20 mg/kg of diltiazem hydrochloride revealed a rise of GPT but it was transient and tended to recover the normal level at the end of experiment.

2. Teratogenicity
The effect of diltiazem hydrochloride on the fetus was examined by the method as specified in "Policy for Assurance of Drug Safety" notified by the Ministry of Health and Welfare of Japan. At the oral dose level of more than 10 mg / kg in ICR-JCL-strain mice and more than 200 mg / kg in Wistar-strain rats, diltiazem hydrochloride caused death of the fetus. At the oral dose level of more than 50 mg / kg in ICR-JCL-strain mice, diltiazem hydrochloride provoked teratogenic effect. At an oral dose of 400 mg/ kg in Wistar-strain rats, diltiazem hydrochloride did not provoke teratogenic effect.

(INDICATION)

- Hypertension. It may be used alone or in combination with other antihypertensive medications, such as diuretics.
- Angina pectoris, Variant angina.

(DOSAGE AND ADMINISTRATION)

For adults, 1 capsule (90 mg as diltiazem hydrochloride) twice a day orally. The dosage may be increased or decreased according to the severity of symptoms. Diltiazem hydrochloride has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem hydrochloride or the concomitant antihypertensives may need to be adjusted when adding one to the other.

(PRECAUTIONS)

1. General precaution:
Since it is described in case - reports that symptoms were aggravated after sudden withdrawal of Calcium- antagonists medication, reduce the dose gradually and observe the symptoms carefully if HERBESSER 90 SR is to be withdrawn. Give patients precaution not to discontinue HERBESSER 90 SR medication without physician's directions.

2. HERBESSER 90 SR is contraindicated to the following patients:
(1) Patients having atrioventricular block 2nd and 3rd degree or sinoatrial block.
(2) Pregnant women and women of pregnant suspicion.
(3) Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
(4) Patients with hypotension (less than 90 mmHg systolic).
(5) Patients who have demonstrated hypersensitivity to the drug.
(6) Patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.
(7) Patients receiving ivabradine hydrochloride.

3. HERBESSER 90 SR is to be carefully administered in the following cases:
(1) Patients with severe bradycardia (below 50 beats/ min.) or 1st degree atrioventricular block.
(2) Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
(3) Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.
(4) Patients with impaired renal or hepatic function.

4. Adverse reactions:
(1) Cardiovascular system:
Dizziness, bradycardia, flush, A-V block may occasionally, and palpitation, edema, ECG abnormality, hypotension may rarely occur. In such cases, the dose should be reduced or medication should be discontinued.
(2) Central nervous system:
Lassitude, headache and heaviness of head may occasionally, and somnolence, insomnia, asthenia may rarely occur.
(3) Liver:
Jaundice and hepatomegaly may rarely occur. The drug should be withdrawn in such cases. Level of GOT, GPT and alkaline phosphatase may be elevated occasionally.
(4) Hypersensitivity:
Hypersensitivity symptoms such as eruption and multiform erythematous eruption may occur infrequently. In such cases, medication should be discontinued.
(5) Gastrointestinal system:
Stomach discomfort, constipation, abdominal pain, heart burn and anorexia may occasionally occur. Soft stool, nausea, diarrhea, thirst and dyspepsia may rarely occur.
(6) Others:
Polyuria may rarely occur.

5. Administration to pregnant women and nursing mothers:
(1) Since animal experiments have proved teratogenic and feticidal effects of diltiazem hydrochloride, HERBESSER 90 SR is contraindicated to pregnant women and women of pregnant suspicion.
(2) It is not recommended to administered HERBESSER 90 SR to nursing mothers since it is reported diltiazem hydrochloride is excreted in human milk. If administration is necessitated, nursing should be avoided.

6. Administration to children:
Safety of HERBESSER 90 SR in children has not been established.

7. Drug interaction:
This product is metabolized mainly by cytochrome P450 3A4 (CYP3A4) metabolizing enzyme.

(1) Contraindications for Co-administration (Do not co-administer with the following.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Ivabradine hydrochloride (Coralan)	Excessive bradycardia may occur.	This product inhibits CYP3A4, the metabolism of ivabradine is inhibited, and the blood concentration of ivabradine is increased. The heart rate reducing effect of ivabradine hydrochloride is potentiated additively.

(2) Precaution for coadministration (HERBESSER 90 SR should be carefully administered in case of concomitant use with the following drugs):

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs with antihypertensive effects (antihypertensive drugs, nitric acid preparation, etc.)	Antihypertensive effects may be intensified. Blood pressure should be measured periodically to adjust the dosage.	Antihypertensive effects may be intensified additively.
Beta blockers (bisoprolol fumarate, propranolol hydrochloride, atenolol, etc.)	Bradycardia, atrioventricular block, sinoatrial block, etc. may occur. Pulse rate should be measured periodically, and electrocardiogram should be performed as needed. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued	Depression of cardiac stimulation and cardiac conduction, negative inotropic effects, and antihypertensive effects may be intensified additively. Particular attention should be given to triple therapy using this product with digitalis preparation and beta blocker or rauwolfia preparation.
Rauwolfia preparations (reserpine, etc.)		
Digitalis preparations (digoxin, methyldigoxin)	Bradycardia, atrioventricular block, etc. may occur. In addition, toxic symptoms (nausea, vomiting, headache, dizziness, abnormal vision, etc.) including above arrhythmic symptoms may occur due to an increase blood concentration of digitalis	Depression of cardiac stimulation and cardiac conduction may be intensified additively. Particular attention should be given to triple therapy using this product with digitalis preparation and beta blocker. This product may be increase

	preparations. Presence or absence of digitalis toxicity should be observed periodically, and electrocardiogram should be performed. In addition, blood concentration of digitalis preparation should be measured as needed. If any abnonnali1ics are observed, the dosage should be reduced or administration should be discontinued.	blood concentrate ions of digitalis preparations.
Antiarrhythmic agents (amiodarone hydrochloride, mexiletine hydrochloride, etc.)	Bradycardia, atrioventricular block, sinus arrest, etc. may occur. Pulse rate should be measured periodically, and electrocardiogram should be performed as needed. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued	Depression of cardiac stimulation and cardiac conduction may be intensified additively.
Fingolimod hydrochloride	Severe bradycardia or heart block may occur by concomitant use of this product during the initiation of fingolimod by hydrochloride.	Both diltiazem hydrochloride and fingolimod hydrochloride may induce bradycardia or heart block.
Dihydropyridine calcium antagonists (nifedipine, amlodipine besilate, etc)	Symptoms (intensified antihypertensive effects, etc.) may occur due to increased blood concentration of dihydropyridine calcium antagonist. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be the discontinued.	This product may inhibit the metabolizing enzyme (cytochrome P450) of these drugs, and increase their blood concentrations.
Simvastatin	Rhabdomyolysis or myopathy may occur due to increased blood concentration of simvastatin. Clinical symptoms should be observed periodically. If any abnormalities are observed,	

	administration should be discontinued	
Theophylline	Symptoms (nausea, vomiting, headache, insomnia, etc.) may occur due to increased blood concentration of theophylline. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued	Diltiazem hydrochloride inhibits the hepatic enzyme (cytochrome P450) responsible for the metabolism of theophylline, which delays the metabolism and reduces the clearance of theophylline.
Cyclosporin	Symptoms (renal disorder, etc.) may occur due to increased blood concentration of cyclosporin. Clinical symptoms should be observed periodically, and blood concentration of cyclosporin should be measured. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued	Diltiazem hydrochloride inhibits the hepatic enzyme (cytochrome P450) responsible for the metabolism of cyclosporin, which results in an increase in the blood concentration of cyclosporin
Tacrolimus hydrate	Symptoms (renal disorder, etc.) may occur due to increased blood concentration of tacrolimus. Clinical symptoms should be observed periodically, and blood concentration of tacrolimus should be measured. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued	This product may inhibit the metabolizing enzyme (cytochrome P450) of these drugs, and increase their blood concentrations.
Carbamazepine	Symptoms (sleepiness, nausea, vomiting, dizziness, etc.) may occur due to increased blood concentration of carbamazepine. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued	Diltiazem hydrochloride inhibits the hepatic enzyme (cytochrome P450) responsible for the metabolism of carbamazepine, which results in an increase in the blood concentration of carbamazepine.

Midazolam	Symptoms (intensified sedative and hypnotic effect, etc.) may occur due to increased blood concentration of midazolam. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	Diltiazem hydrochloride inhibits the hepatic enzyme (cytochrome P450) responsible for the metabolism of midazolam, which results in an increase in the blood concentration of midazolam.
Selegiline hydrochloride	Effects and toxicity of selegiline hydrochloride may be intensified. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	
Cilostazol	Effects of cilostazol may be intensified. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	
Vinorelbine tartrate	Effects of vinorelbine tartrate may be intensified. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	
Apixaban	Effects of apixaban may be intensified. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	
Phenytoin	Symptoms (ataxia, dizziness, nystagmus, etc.) may occur due to increased blood concentration of phenytoin.	This product may inhibit the metabolizing enzyme (cytochrome P450) of phenytoin and increase blood

	Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued. Effect of this product may be attenuated.	concentrations of phenytoin. In addition, phenytoin may stimulate metabolism of this product, and decrease blood concentrations of this product.
Cimetidine	Symptoms (intensified antihypertensive effect, bradycardia, etc.) may occur due to increased blood concentration of this product. Clinical symptoms should be observed periodically, and electrocardiogram should be performed as needed. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	These drugs may inhibit the metabolizing enzyme (cytochrome P450) of this product, and increase blood concentration of this product.
HIV protease inhibitors (ritonavir, saquinavir mesylate, etc.)		
Rifampicin	Effects of this product may be attenuated. Clinical symptoms should be observed periodically, and if possible blood concentration of this product should be measured. If any abnormalities are observed, appropriate therapeutic measures such as changing to other drugs or increasing the dosage of this product should be taken.	Rifampicin may induce the metabolizing enzyme (cytochrome P450) of this product, and decrease blood concentration of this product.
Anesthetics drugs (isoflurane, enflurane, halothane, etc.)	Bradycardia, atrioventricular block, sinus arrest, etc. may occur. Electrocardiogram should be monitored. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	Depression of cardiac stimulation and cardiac conduction may be intensified additively.
Muscle relaxants (pancuronium bromide, vecuronium bromide, etc.)	Effects of muscle relaxants may be intensified. Caution should be exercised to muscle relaxants action. If any abnormalities are observed, the dosage should be reduced or administration should be	This product may inhibit the acetylcholine release from the presynaptic terminals at the neuromuscular junction.

	discontinued.	

(HANDLING)

Caution:

- Dispense by physician's prescription or direction
- Keep out of reach from children
- Swallow the capsules without chewing or opening

Storage: Store in a tight and light-resistant container at below 30° C.

(PRESENTATION)

- Box of 10 blister sheets of 10 capsules

ON DOCTOR'S PRESCRIPTION ONLY

Under license from:
Mitsubishi Tanabe Pharma Corporation
Osaka, Japan

Manufactured by:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

Product Registrant:
Mitsubishi Tanabe Pharma Singapore Pte Ltd.

Marketed by:
Pharmaforte Singapore Pte Ltd