SUSTAINED RELEASE CA-ANTAGONIST

HERBESSER® R100

HERBESSER® R200

(Diltiazem hydrochloride)

Caution: Use only pursuant to the prescription or directions of a physician, etc.

Storage
Store at below 30"C. Avoid humidity after opening.

Expiration date
Indicated on the package and container.

CONTRAINDICATIONS (HERBESSER R is contraindicated in the following patients.)

(1) Patients with severe congestive heart cardiac failure [Symptoms of cardiac failure may be aggravated]

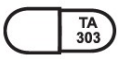
(2) Patients with second or third degree atrioventricular block or sick sinus syndrome (persistent sinus bradycardia) (less than 50 beats/ minute), sinus arrest, sinoatrial block, etc.) [Depression of cardiac stimulation and cardiac conduction may occur excessively].

(3) Patients with a history of hypersensitivity to any of the ingredients of this product.

(4) Pregnant women or women who may possibly be pregnant [See "Use during pregnancy, Delivery or lactation" section]

(5) Patients receiving ivabradine hydrochloride. [See “Drug Interactions” section.]

DESCRIPTION

Brand name	HERBESSER R100	HERBESSER R200
Active Ingredient (per capsule)	Diltiazem hydrochloride	
	100mg	200mg
Dosage form (Type of capsule)	Hard capsule (No.4)	Hard capsule (No.2)
Color (Cap/Body)	White/White	Red/White
Description of contents	White to pale yellowish white granules	
Appearance		
Size (mm)	Length: 14.2 mm Diameter: 5.4 mm	Length: 17.7 mm Diameter: 6.4 mm
Weight	0.17g	0.32g
Identification code	TA303	TA304

INDICATIONS

- Essential hypertension (mild to moderate)
- Angina pectoris, variant angina pectoris

DOSAGE AND ADMINISTRATION

- Essential hypertension (mild to moderate)

Usually, for adults, I00 mg to 200 mg of diltiazem hydrochloride is orally administered once daily. The dosage may be adjusted according to the patient’s age and symptoms.

- Angina pectoris, variant angina pectoris

Usually, for adults, 100 mg of Diltiazem hydrochloride is orally administered once daily. If the effect is insufficient, the dosage may be increased to 200 mg once daily.

PRECAUTIONS

1. Careful Administration (HERBESSER should be administered with care in the following patients.)

1) Patients with congestive cardiac failure. [Symptoms of cardiac failure may be aggravated.]
2) Patients with severe bradycardia (less than 50 beats/min) or first grade atrioventricular block. [Depression of cardiac stimulation and cardiac conduction may occur excessively.]
3) Patients with excessively low blood pressure [Blood pressure may be further decreased.]
4) Patients with severe hepatic or renal impairment. [The metabolism excretion of this product may be prolonged, and effects may be intensified.]

2. Important Precautions

1) It has been reported that abrupt cessation of calcium antagonist may aggravate the patient's symptoms. In case where **cessation** of this product is required, the dosage should be **reduced gradually** under careful observation of the patient. Patients should be instructed not to discontinue taking this product without consulting physicians.
2) Since dizziness, etc. may occur due to the antihypertensive action of this product, patients should be cautioned against engaging in potentially hazardous activities, such as working at altitude or driving motor vehicles.
3) Prolonged QT and ventricular arrhythmia have been reported in coadministration of terfenadine with other antiarrhythmic agents (disopyramide phosphate)

3. Drug Interactions

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 R should be administered with care when coadministered 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.) Rauwolfia preparations (reserpine, 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.
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 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.	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 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	Depression of cardiac stimulation and cardiac conduction may be intensified additively.

	discontinued	
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, 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	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.

	dosage should be reduced or administration should be discontinued	
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	Diltiazem hydrochloride may inhibit the metabolizing enzyme (cytochrome P450) of this drug, and increase its blood concentration.
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.	Diltiazem hydrochloride may inhibit the metabolizing enzyme (cytochrome P450) of this drug, and increase its blood concentration.
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. 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.	This product may inhibit the metabolizing enzyme (cytochrome P450) of phenytoin and increase blood 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 discontinued.	This product may inhibit the acetylcholine release from the presynaptic terminals at the neuromuscular junction.

4. Adverse Reactions

Adverse reactions were reported in 74 (2.1%) of 3,577 patients. The major adverse reactions were cardiovascular symptoms in 0.7% (bradycardia in 0.2%, atrioventricular block in 0.1%, facial flushing in 0.1%, etc.), gastrointestinal symptoms in 0.6% (constipation in 0.2%, nausea in 0.2%, stomach discomfort in 0.1%, etc.), headache and headache dull in 0.4%, hypersensitivity in 0.3%, etc. (at the time of completion of reexamination).

1) Clinically significant adverse reactions (rarely:<0. 1%, incidence unknown because of spontaneous reports)

(1) **Complete atrioventricular block, severe bradycardia** (early symptom: bradycardia, dizziness, light- headedness, etc.) may occur rarely. If any abnormalities are observed, administration should be discontinued and atropine sulfate hydrate, isoprenaline, etc. should be administered or appropriate therapeutic measures such as cardiac pacing should be taken as needed.

(2) **Congestive cardiac failure** may occur. If any abnormalities are observed, administration should be discontinued, and appropriate therapeutic measures such as administration of cardiotonic drug, etc. should be taken.

(3) **Oculomucocutaneous syndrome (Steven-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythroderma (exfoliative dermatitis), acute generalized exanthematous**

pustulosis may occur. If erythema, blister, pustule, pruritis, fever, enanthema, etc. occur, administration should be discontinued, and appropriate therapeutic measures should be taken.
(4) **Hepatic function disorder or jaundice** with increased AST (GOT), ALT(GPT) or γ-GTP may occur. The patient's conditions should be observed carefully. If any abnormalities are observed, administration should be discontinued, and appropriate therapeutic measures should be taken.

2) Other adverse reactions
If any adverse reactions are observed, appropriate therapeutic measures such as discontinuation of treatment should be taken.

Incident / Type	5% > ≥0.1%	<0.1%	Incidence unknown
Cardiovascular	Bradycardia, atrioventricular block, facial flushing, dizziness	Sinus arrest, decreased blood pressure, palpitation, chest pain, oedema	Sinoatrial block
Psychoneurologic	Malaise, headache, headache dull.	Cramps in the calves, feelings of weakness, sleepiness, insomnia	Parkinsonian- like symptom
Hepatic	Increased AST (GOT), increased ALT(GPT)	Jaundice	Increased AI-P, increased LDH, increased γ-GTP, hepatic hypertrophy
Hypersensitivity	Rash	Pruritis, multiforme erythematous, rash, urticaria.	Photosensitivity, pustule
Gastrointestinal	Stomach discomfort, constipation. abdominal pain, heartburn, anorexia, nausea	Soft stool, diarrhea, thirst.	-
Hematologic	-	-	Decreased platelets count, decreased white blood cell count
Other	-	-	Gingival hypertrophy, gynaecomastia, numbness

5. Use in the Elderly
Excessive decrease in blood pressure is generally considered undesirable in elderly patients. Therefore, HERBESSER should be administered with care such as starting from a lower dosage while carefully monitoring the patient's condition.

6. Use during Pregnancy, Delivery or Lactation
1) HERBESSER is contraindicated in pregnant women or women who may possibly be pregnant. [Animal studies have shown teratogenicity (mice: skeletal abnormality, appearance abnormality) and embryo toxicity (mice, rats: fatality).]

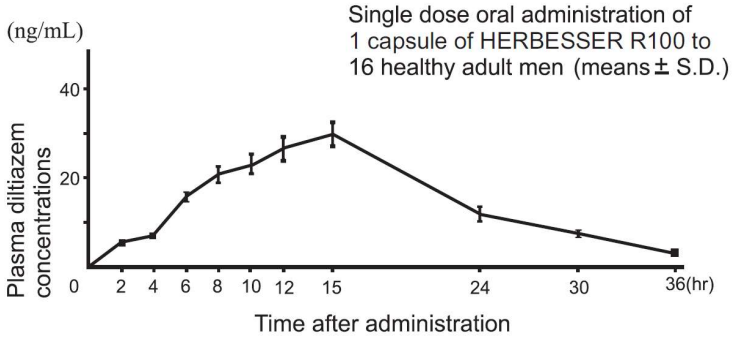
2) Use of this product in lactating women is not recommended. If treatment with this product is judged to be essential, breast feeding must be discontinued during treatment.
[It has been reported that diltiazem is excreted in human breast milk.]

7. Pediatric Use
The safety of HERBESSER in children has not been established.

8. Overdosage
Symptoms:
Bradycardia, complete atrioventricular block, cardiac failure, hypotension, etc. may occur after overdosage of HERBESSER. These symptoms have been also reported as adverse reactions.
Treatment:
In case of overdosage, administration should be discontinued, and gastric lavage should be performed to remove the product as needed, and the following appropriate therapeutic measures should be taken.
1) Bradycardia, complete atrioventricular block
Atropine sulfate hydrate, isoprenaline, etc. should be administered or cardiac pacing should be taken.
2) Cardiac failure, hypotension
Cardiotonic drug, vasopressor, infusion, etc. should be administered or assisted circulation should be performed.

9. Precautions concerning Use
1) Precautions regarding dispensing:
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the PTP sheet prior to use. [It was reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]
2) Precautions during oral administration:
This product should be taken without opening and chewing the capsule.

PHARMACOKINETICS
1. Plasma concentration
Plasma concentration of this product after oral administration of one capsule of HERBESSER R Capsules 100 mg to healthy male adults reached maximum at about 14 hours after the administration, and the elimination half-life was about 7 hours.



2. Metabolism
When this product was administered orally to healthy male adults, the main metabolic pathways were oxidative deaminization, oxidative demethylation, deacetylation, and conjugation.

CLINICAL STUDIES

Clinical efficacy

The usefulness of this product was proven for essential hypertension, angina pectoris and variant angina in clinical studies including a double-blind comparative clinical trials study using diltiazem hydrochloride (HERBESSER Tablets 30) as a control.

Diseases	Efficacy rate	No. of patients	No. of patients evaluated as effective
Essential hypertension	73.9%	222	164 (“decreased”or better)
Angina pectoris	84.7%	124	105 (“moderate improvement” or better)
Variant angina pectoris	90.2%	51	46 (“moderate improvement” or better)

PHARMACOLOGY

Diltiazem hydrochloride dilates blood vessels, improves myocardial ischaemia, and exerts antihypertensive effect by inhibiting calcium channel influx to cells in vascular smooth muscles such as coronary vessels, peripheral vessels, etc.

1. Action on myocardial ischaemia

1) Improvement of myocardial oxygen demand and supply balance

(1) It dilates large coronary vessels and collateral channels, and increases blood flow to myocardial ischaemic lesions (dogs).

(2) It inhibits coronary artery spasm (monkeys and humans).

(3) It decreases myocardial oxygen consumption without decreasing cardiac output by afterload reduction due to peripheral vasodilation and decreased heart rate (dogs).

2) Myocardial protective action

It maintains cardiac function and myocardial energy metabolism, and reduces the extension of infarct lesions by inhibiting calcium channel influx to cells at the time of myocardial ischaemia (rats).

2. Action on blood pressure

1) It has almost no effect on normal blood pressure, while decreases high blood pressure gradually (rats and humans) , and inhibits exercise-induced blood pressure elevation (humans).

2) It does not decrease cerebral and renal blood flow, while decreases blood pressure (dogs and humans).

3) It inhibits myocardial and vascular hypertrophies along with decreased blood pressure (rats).

3. Effects on cardiac stimulation and cardiac conduction

It slightly prolongs sinus node spontaneous cycle length and slows atrioventricular nodal conduction (AH interval), while it does not affect His- Purkinje system conduction (HV interval) (dogs and humans).

PHYSIOCHEMISTRY

Nonproprietary name:

Diltiazem Hydrochloride (JAN)

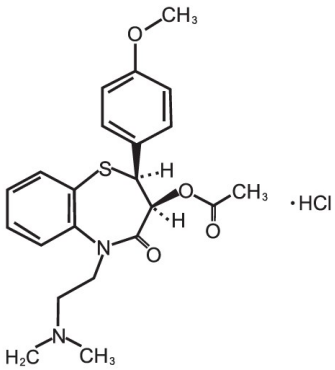
Diltiazem (INN)

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

Molecular formula:
$C_{22}H_{26}N_2O_4S \cdot HCl$: 450.98

Structural formula:



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 acetic anhydride or in ethanol (99.5), and practically insoluble in diethyl ether.
- Optical rotation $[\alpha]^{20}_D$: + 115 to - + 120° (After drying, 0.20 g, water, 20 mL, 100 mm).
- Melting point: 210 - 215° C (decomposition)

PACKAGING
HERBESSER R100:
Boxes of 30 capsules (10 capsules x 3) in PTP
Boxes of 100 capsules (10 capsules x 10) in PTP

HERBESSER R200:
Boxes of 30 capsules (10 capsules x 3) in PTP
Boxes of 100 capsules (10 capsules x 10) in PTP

Beads Manufactured by:
Mitsubishi Tanabe Pharma Factory Ltd.
Yamaguchi, Japan

Beads Imported, Encapsulated and Packed by:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

Under license from:
Mitsubishi Tanabe Pharma Corporation
Osaka, Japan

Product Registrant:
Mitsubishi Tanabe Pharma Singapore Pte. Ltd.

Marketed by:
Pharmaforte Singapore Pte Ltd