-CA-ANTAGONIST-

HERBESSER®
HERBESSER®60
(Diltiazem hydrochloride)

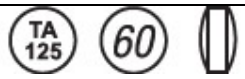
Caution - Use only pursuant to the prescription or directions of a physician, etc

Storage
Store at below 30ºC. Avoid humidity after opening

Expiration date
Indicated on the package and container.

CONTRAINDICATIONS (HERBESSER and HERBESSER 60 are contraindicated in the following patients.)
I) Patients with severe congestive heart failure. [The symptoms of heart failure may be exacerbated.]
2) Patients with 2nd- or 3rd-degree atrioventricular block or sick sinus syndrome (continuous sinus bradycardia (less than 50 beats/minute), sinus arrest, sinoatrial block, etc.) [Excessive inhibition of sinus rhythm and cardiac conduction may occur.]
3) Patients with a history of hypersensitivity to any of the ingredients in the drug.
4) Pregnant women or women who may possibly be pregnant, etc. [See PRECAUTIONS - Use during Pregnancy, Delivery or Lactation.]
5) Patients receiving ivabradine hydrochloride. [See "Drug Interactions" section.]

DESCRIPTION

Brand name	**HERBESSER**	**HERBESSER 60**
Ingredient content (content per tablet)	Diltiazem hydrochloride	
	30mg	60mg
Dosage form	Plain tablets	
Color	White	
Appearance		
Size	Diameter: 8.0 mm Thickness: 3.5 mm	Diameter: 8.0 mm Thickness: 3.5 mm
Weight	0.19g	0.185g
Identification code	TA120	TA125

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

DOSAGE AND ADMINISTRATION
- Angina pectoris, variant angina pectoris
The usual adult dosage for oral use is 30 mg of diltiazem hydrochloride three times a day (90 mg/day). The dosage may be increased to 60 mg three times a day (180 mg/day), if necessary.
- Essential hypertension (mild to moderate)
The usual adult dosage for oral use is 30 to 60 mg of diltiazem hydrochloride three times a day (90 - 180 mg/day). The dosage may be adjusted depending on the patient's age and symptoms.

PRECAUTIONS

1. Careful Administration (HERBESSER and HERBESSER 60 should be administered with care in the following patients.)

1) Patients with congestive heart failure. [The symptoms of heart failure may be exacerbated.]
2) Patients with severe bradycardia (less than 50 beats/minute) or 1st-degree atrioventricular block. [Excessive inhibition of sinus rhythm and cardiac conduction may occur.]
3) Patients with severe hypotension. [The blood pressure may be further reduced.]
4) Patients with severe hepatic and renal dysfunction. [The action of the drug may be enhanced due to its delayed metabolism and excretion.]

2. Important Precautions

1) It has been reported that abrupt withdrawal of calcium antagonists may result in aggravation of symptoms. If HERBESSER and HERBESSER 60 are withdrawn, the dosage should be gradually reduced and the patient should be carefully monitored. The patient should be instructed not to discontinue taking the drug without consulting a physician.
2) Since dizziness, etc. due to hypotensive effect may occur, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as driving a car, working at heights, or operating machinery, etc.
3) It has been reported that concomitant use of other antiarrhythmic agent (disopyramide phosphate) with terfenadine may result in QT interval prolongation and ventricular arrhythmia.

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)

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) Precautions for co-administration (HERBESSER and HERBESSER 60 should be administered with care when co-administered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Drugs with anti-hypertensive Effects (antihypertensive drugs, nitric acid preparations, etc.)	Antihypertensive effects may be intensified. Blood pressure should be measured periodically to adjust the dosage.	Antihypertensive effects may be intensified additively.

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 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.	
β-Blocking agents (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, metildigoxin)	Bradycardia, atrioventricular block, etc. may occur. Symptoms of digitalis toxicity (nausea, vomiting, headache, dizziness, abnormal vision, etc.) including such arrhythmias may occur due to an increase in the blood concentration of the digitalis preparations. Presence or absence of digitalis toxicity should be observed periodically, and electrocardiogram should be performed. In addition, blood concentrations of digitalis preparation should be measured 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. Particular attention should be given to triple therapy using this product with digitalis preparation and beta blocker. This product may increase blood concentrations of digitalis preparations.
Antiarrhythmic drugs (amiodarone hydrochloride,	Bradycardia, atrioventricular block, sinus arrest, etc. may occur. Pulse rate should be	Depression of cardiac stimulation and cardiac conduction may

mexiletine hydrochloride, etc.)	measured periodically, and electrocardiogram should be performed as needed. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	be intensified additively.
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.
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.	
Cyclosporin	Symptoms (renal disorders, etc.) due to an increase in the blood concentration of cyclosporin may occur. Clinical symptoms should be observed periodically, and blood concentration of ciclosporin 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 disorders, etc.) due to an increased in the 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	Diltiazem hydrochloride inhibits the hepatic enzyme (cytochrome P450) responsible for the metabolism of carbamazepine, which results in an increase in the blood

	abnormalities are observed, the dosage should be reduced or administration should be discontinued.	concentration of carbamazepine.
Phenytoin	Symptoms (ataxia, dizziness, nystagmus, etc.) due to an increase in the 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. Effects of this product may be attenuated.	This product may inhibit the metabolizing enzyme (cytochrome P450) of phenytoin, and increase blood concentration of phenytoin. In addition, phenytoin may stimulate metabolism of this product, and decrease blood concentration of this product.
Midazolam	Symptoms (intensified sedative and hypnotic effects, 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.
Cimetidine HIV Protease inhibitors (ritonavir, saquinavir mesylate, etc.)	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.
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 induces the hepatic enzyme (cytochrome P450) responsible for the metabolism of diltiazem hydrochloride, which results in a decrease in the blood concentration of this product..
Anesthetics (isoflurane, enflurane, halothane, etc.)	Bradycardia, atrioventricular block, sinus arrest, etc. may occur.	Depression of cardiac stimulation and cardiac

	Electrocardiogram should be monitored. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	conduction may be intensified additively.
Muscle relaxants (pancuronium bromide, vecuronium bromide)	Effect of muscle relaxants may be intensified. Caution should be exercised to muscle relaxant action. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	This product may inhibit the acetylcholine release from presynaptic terminals at the neuromuscular junction.
Fingolimod hydrochloride	Severe bradycardia or heart block may occur by concomitant use of this product during the initiation of fingolimod hydrochloride.	Both diltiazem hydrochloride and fingolimod hydrochloride May induce bradycardia or heart block.
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.	
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.	
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.	

4. Adverse Reactions

Adverse reactions to HERBESSER and HERBESSER 60 were reported in 442 (4.6%) of 9,630 patients treated. The most frequent adverse reactions were observed in gastrointestinal system 1.4 % (stomach discomfort 0.2%, constipation 0.2%, abdominal pain 0.1%, etc.) and in cardiovascular system 1.4% (dizziness 0.5%, bradycardia 0.4%, facial hot flushes 0.2%, atrioventricular block 0.2%, etc.), hypersensitivity 1.2%, headache 0.2%, etc. (Data collected from the time of approval up to December 1990)

1) **Clinically significant adverse reactions** (rarely: <0.1%, unknown: the incidence of adverse reactions on the basis of spontaneous reports is unknown)

(1) **Complete atrioventricular block, severe bradycardia** (initial symptoms: bradycardia, dizziness, light-headed, etc.), etc., may occur rarely (<0.1%). If any abnormalities are observed, the drug should be discontinued and appropriate measures, such as administration of atropine sulfate, isoproterenol, etc., and/or application of cardiac pacing, etc., if necessary, taken.
(2) **Congestive heart failure*** may occur. If any abnormalities are observed, the drug should be discontinued and appropriate measures, such as administration of cardiac stimulants, taken.
(3) **Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythroderma (exfoliative dermatitis)***, **acute generalised exanthematous pustulosis** may occur. If erythema, blisters, pruritus, fever, enanthema, etc. are observed, the drug should be discontinued and appropriate measures 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 measures, such as discontinuing administration, should be taken.

	Incidence unknown	5%> ≥0.1%	<0.1%
Cardiovascular	Sinoatrial block	Bradycardia, atrioventricular block, facial hot flushes, dizziness,	Sinus arrest, decreased Blood pressure, palpitation, chest pain, edema,
Psychoneurologic	Parkinsonism-like symptoms •	Malaise, headache, dull headache	Muscle cramps, weakness, sleepiness, insomnia
Hepatic	Increased Al-P, increased LDH, increased γ-GTP, hepatic hypertrophy	Increased AST (GOT) and ALT (GPT)	Jaundice
Hypersensitivity	Photosensitivity, pustule	Rash	Pruritus, multiform erythema-like eruption, urticaria,
Gastrointestinal	-	Stomach discomfort, constipation, abdominal pain, heartburn, anorexia, nausea	Loose stools, diarrhea, thirst,
Hematologic	Thrombocytopenia*, leucopenia*	-	-
Other	Gingival hyperplasia, Gynecomastia, numbness	-	-

* Since the data are based on spontaneous reports, the incidence of adverse reactions is unknown.

5. Use in the Elderly

An excessive reduction in blood pressure is undesirable in elderly patients. Therapy should therefore be instituted with special care, starting at a reduced dosage with careful monitoring of the patient's condition.

6. Use during Pregnancy, Delivery or Lactation

1) HERBESSER and HERBESSER 60 are contraindicated in pregnant women or women who may possibly be pregnant. [Animal studies have shown that the drug has teratogenic effects (mice: skeletal abnormalities, dysplasias) and embryo toxicity (mice, rats: death).]

2) It is advisable to avoid using the drug in lactating mothers. If use of the drug is judged to be essential, breast feeding should be discontinued during treatment. [It has been reported that diltiazem hydrochloride is excreted in breast milk.]

7. Pediatric Use

The safety of HERBESSER and HERBESSER 60 in children has not been established.

8. Overdosage

Symptoms:

Overdosage my cause bradycardia, complete atrioventricular block, heart failure, hypotension, etc. These symptoms are also reported as adverse reactions.

Treatments:

In the event of overdosage, the administration of HERBESSER and HERBESSER 60 should be discontinued and the following appropriate measures taken, while removing the drug by gastric lavage, etc. if necessary.

1) Bradycardia, complete atrioventricular block:

Administer atropine sulfate, isoproterenol, etc., and/or apply cardiac pacing.

2) Heart failure, hypotension:

Administer intravenous fluids, an inotropic agent, a pressor agent, etc., and/or institute assisted circulation.

9. Precautions concerning Use

1) Precautions regarding dispensing:

When HERBESSER and HERBESSER 60 are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been 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.]

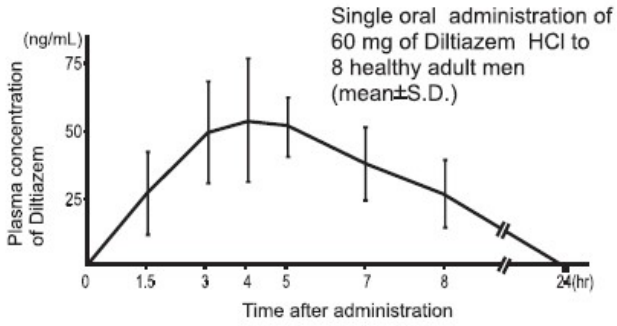
2) Precautions during administration:

Patients should be instructed not to chew the tablets (Sustained release property may be reduced)

PHARMACOKINETICS

1. Blood concentration

When 2 tablets of HERBESSER (60 mg of diltiazem hydrochloride) were orally administered to healthy adult men, its plasma concentration reached a maximum 3 to 5 hours after administration, and decreased thereafter with a half-life of about 4.5 hours. On daily oral administrations, the plasma concentration of diltiazem reached a steady state 2 days after the start of administration. During the long-term, repeated oral administration of 90 mg (30 mg x 3)/day of diltiazem hydrochloride to patients, its plasma concentration 2 to 4 hours after administration was about 40 ng/mL.



2. Metabolism

In case of oral administration to healthy adult men, diltiazem hydrochloride was metabolized mainly by oxidative deamination, oxidative demethylation, deacetylation, and conjugation.

CLINICAL STUDIES

1. Angina pectoris, variant angina pectoris

The usefulness of HERBESSER and HERBESSER 60 in the treatment of angina pectoris was demonstrated by double blind comparative clinical trials, single blind comparative clinical trials, and open labeled clinical trials. The usefulness of the drug in the treatment of variant angina pectoris was demonstrated by open labeled clinical trials , including investigation with the Holter electrocardiogram.

2. Hypertension

The usefulness of HERBESSER and HERBESSER 60 in the treatment of essential hypertension was demonstrated by four double blind comparative clinical trials with a placebo, reserpine, and propranolol as the control drugs.

PHARMACOLOGY

The therapeutic benefits achieved with diltiazem hydrochloride, 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 ions into the smooth muscle cells of the coronary and peripheral blood vessels.

1. Action on myocardial ischemia

1) Improving action on the balance of myocardial oxygen demand and supply

(1) Diltiazem hydrochloride increases coronary blood flow into the myocardial ischemic region by dilating the large coronary artery and the collateral channels (dogs).

(2) Diltiazem hydrochloride inhibits coronary artery spasms (monkey, humans).

(3) Diltiazem hydrochloride decreases myocardial oxygen consumption without decreasing cardiac output by decreasing the afterload and heart rate though peripheral vasodilation (dogs).

2) Action on myocardial protection

Diltiazem hydrochloride maintains cardiac function and myocardial energy metabolism, and reduces the infarct size by inhibiting excess calcium ion influx into the cells under myocardial ischemia (rats).

2. Action on blood pressure

(1) Diltiazem hydrochloride lowers an elevated blood pressure gradually, although it hardly affects the normal blood pressure (rats, humans), and it suppresses the elevation of blood pressure induced by exercise load (humans).

(2) Diltiazem hydrochloride lowers blood pressure without decreasing the cerebral and renal blood flow (dogs, humans).

(3) Diltiazem hydrochloride suppresses myocardial and vascular hypertrophy while lowering blood pressure (rats).

3. **Action on sinus rhythm and cardiac conduction system**
   Diltiazem hydrochloride prolongs slightly spontaneous sinus rhythm intervals and the A-H conduction time, but it does not affect the H-V conduction time (dogs, humans).

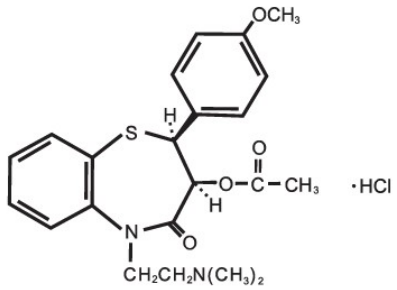
PHYSIOCHEMISTRY

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:
- It occurs as white crystals or crystalline powder, and 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 and in ethanol (99.5), and practically insoluble in diethyl ether.
- Optical rotation $[\alpha]^{20}_D$: + 115 - + 120°(after drying, 0.20 g, water, 20 mL, 100 mm)
- Melting point: 210- 215°C (decomposition)

PACKAGING

HERBESSER:
Boxes of 100 tablets (10 tablets x 10) in PTP
Boxes of 1000 tablets (10 tablets x 100) in PTP

HERBESSER 60:
Boxes of 100 tablets (10 tablets x 10) in PTP
Boxes of 1000 tablets (10 tablets x 100) in PTP

Under license from:
Mitsubishi Tanabe Pharma Corporation
Osaka, Japan

Manufactured by:
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia