* Date of Revision: May 2024
Ca-antagonist

# HERBESSER®R100
# HERBESSER®R200

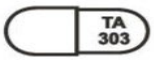
(Diltiazem hydrochloride)
Sustained Release Capsules

MAL
Mitsubishi Tanabe Pharma

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

(1) Patients with severe congestive 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 and women who may possibly be pregnant [See "Use during Pregnancy, Delivery or Lactation" section].
(5) Patients receiving asunaprevir-containing product, ivabradine hydrochloride, or lomitapide mesylate [See “Drug Interactions” section].

## DESCRIPTION

| Product name | HERBESSER R100 | HERBESSER R200 |
|---|---|---|
| Content (per capsule) | Diltiazem hydrochloride | |
| | 100 mg | 200 mg |
| Dosage from (Capsule No.) | Hard capsule (No.4) | Hard capsule (No.2) |
| Color (Cap/Body) | White/White | Red/White |
| Content | White to pale yellowish white beads | |
| Appearance |   |   |
| Size (mm) | Length: 14.3 mm (14.0 – 14.6 mm) | Length: 18 mm (17.7 – 18.3 mm) |
| Weight (g) | 0.168 g (0.162 – 0.175 g) | 0.321 g (0.308 – 0.334 g) |
| Identification code | TA303 | TA304 |

## INDICATIONS

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

## DOSAGE AND ADMINITRATION

- Essential hypertension (mild to moderate)
  Usually, for adults, 100 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 to 200 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 and 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 antagonists 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 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 |
|---|---|---|
| Asunaprevir<br>Daclatasvir hydrochloride/ asunaprevir / beclabuvir hydrochloride | The blood concentration of asunaprevir increased.<br>Hepatobiliary disorder may occur and become severe. | This product inhibits CYP3A, and the metabolism of these drugs is inhibited. |
| Ivabradine hydrochloride | Excessive bradycardia may occur. | This product inhibits CYP3A, 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. |
| Lomitapide mesylate | The blood concentration of lomitapide mesylate may be markedly increased. | This product inhibits CYP3A, and the metabolism of lomitapide is inhibited. |

**(2) Precautions for coadministration (HERBESSER should be administered with care when co-administered 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.)<br>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 increased blood concentration of digitalis preparation.<br>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 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 be increase blood concentrations 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. |
| Aprindine hydrochloride | Symptoms (bradycardia, atrioventricular block, sinus arrest, tremor, dizziness, light- | Each drug may affect a common metabolizing enzyme (cytochrome P450), and increase |

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| | headedness, etc.) may occur due to increased blood concentrations of both drugs.<br>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. | blood concentration of each drugs |
| 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. | |
| Triazolam | Symptoms (prolonged sleeping time, etc.) may occur due to increased blood concentration of triazolam. Clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued. | |
| 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. | |
| 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 | |

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| | administration should be discontinued. | |
| 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. | |
| 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. | |
| 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. | |
| 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. | |
| 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. | |
| Tacrolimus hydrate | Symptoms (renal disorder, etc.) may occur due to increased blood concentration of tacrolimus. Clinical symptoms should be observed periodically, and blood | |

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| | concentration of tacrolimus should be measured. 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 concentration of this product |
| Cimetidine<br>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 may induce the metabolizing enzyme (cytochrome P450) of this product, and decrease blood concentrations 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 re-examination).

**(1) Clinically significant adverse reactions** (rarely: <0.1%, no adverb: 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.

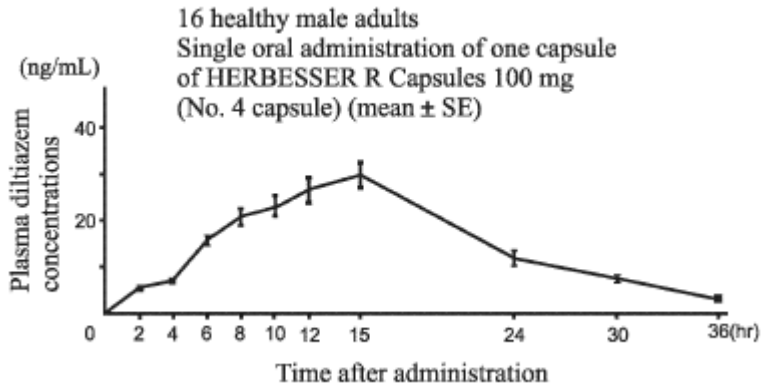
| Incidence / Type | 5% > ≥ 0.1% | < 0.1% | Incidence unknown |
|---|---|---|---|
| **Cardiovascular** | Bradycardia, atrioventricular block, facial flushing, dizziness | Sinus arrest, decreased blood pressure, palpitation, chest pain, oedema | Sinoatrial block |
| **Psychoneurotic** | Malaise, headache, headache dull | Cramps in the calves, feelings of weakness, sleepiness, insomnia | Parkinsonian-like symptom |
| **Hepatic** | Increased AST (GOT), increased ALT(GPT) | Jaundice | Increased Al-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 he 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) HERHESSER should not be administered to pregnant women or women who may possibly be pregnant. [Animal studies have shown teratogenicity (mice: skeletal abnormality, appearance abnormality) and embryotoxicity (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 patients to remove the drug from the PTP sheet prior to use. [It was reported that, if the PTP sheet is swallowed, the sharp comers 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.[1)]




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

## 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 study using diltiazem hydrochloride (HERBESSER tablets 30) as a control.[3-5)]

| 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 | 90.2% | 51 | 46 (“moderate” improvement or better) |

## PHARMACOLOGY

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

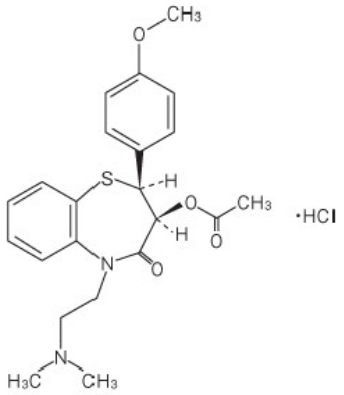
1. **Action on myocardial ischemia**
   1) **Improvement of myocardial oxygen demand and supply balance**
      (1) It dilates large coronary vessels and collateral channels, and increases blood flow to myocardial ischaemic lesion (dogs).[6-9)]
      (2) It inhibits coronary artery spasm (monkeys and humans).[10,11)]
      (3) It decreases myocardial oxygen consumption by afterload reduction due to peripheral vasodilation and decreased heart rate without decreasing cardiac output (dogs).[12)]
   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).[13)]

2. **Action on blood pressure**
    1) It has almost no effect on normal blood pressure, while decreases high blood pressure gradually (rats and humans)[14-16], and inhibits exercise-induced blood pressure elevation (humans).[17]
    2) It does not decrease cerebral and renal blood flow, while decreases blood pressure (dogs and humans).[18-21]
    3) It inhibits myocardial and vascular hypertrophies along with decreased blood pressure (rats).[22]
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 effect His-Purkinje system conduction (HV interval) (dogs and humans).[12,23,24]

## PHYSICOCHEMISTRY

**Nonproprietary name:**
Diltiazem Hydrochloride (JAN)
Diltiazem (INN)

**Chemical name:**
(2S,3S)-5-[2-(Dimethylamino) ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetahydro-1,5-benzothiazepin-3-yl-acetate monohydrochloride




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

Description:

- Diltiazem hydrochloride occurs as white crystals or crystalline powder. It is odorless.
- It is very soluble in formic acid, feely 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 $[\alpha]_D^{20}$ : + 115 - + 120° (after drying, 0.20 g, water, 20 mL, 100 mm).
- Melting point: 210 - 215°C (with decomposition)

## STORAGE AND HANDLING

Storage : Do not store above 30°C. After opening, avoid humidity.
Shelf-life : Please see blister and outer carton

## MODE OF ADMINISTRATION

Oral

**PACKAGING**
**HERESSER R100:**
Boxes of 30 capsules (10 capsules x 3) in press through packages
Boxes of I00 capsules (10 capsules x I0) in press through packages

**HERBESSER R200:**
Boxes of 30 capsules (10 capsules x 3) in press through packages
Boxes of 100 capsules (10 capsules x 10) in press though packages

**REFERENCES**

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