ARTWORK PANEL

PKM.T-002 • Tag Artwork Panel • Ver.02 • October 2017

item code	version	revision	tanggal/date	material		
TN-028	04	08	03/06/2020	HVS 60 gr		
customer: PT Mitsubishi Tanabe Pharma Indonesia				ukuran/size: 185 x 840 mm	scale: 100%	page: 1 of 1
judul/title: Brochure Herbesser Powder Injection MTID				colour: Black, cutting line	coating: -	drawing by: Agus Wilmansyah

150 milimeter measuring bar

arya wira mediatama

SIGNATURE PANEL Status : ☐ Approve ☐ Revise ☐ Other :

date date date date

Depan / *front*

185 mm

15 mm 8 mm 15 mm

35 mm 8 mm 19 mm 8 mm

Mitsubishi Tanabe Pharma

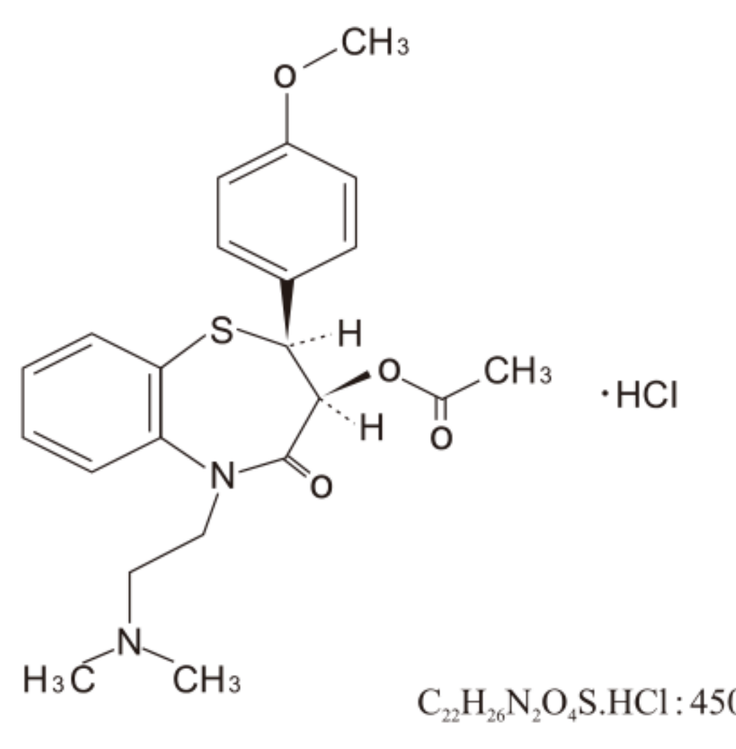
Calcium - Antagonist

HERBESSER® Powder Injection

(COMPOSITION AND DESCRIPTION)

Physicochemical properties of active ingredient

- International non-proprietary name : Diltiazem Hydrochloride
- Chemical name : (2*S*,3*S*)-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 (99.5) and in acetic anhydride, 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).

- Description of HERBESSER® Powder Injection
  Freeze-dried product. This is solution for injection to be dissolved in physiological saline or glucose injection before use.

Description of solution contained in one vial when dissolved in 5 mL water for injection	
Product's name	HERBESSER® DILTIAZEM HCl Powder Injection 50 mg
Appearance	Colorless and clear
pH	5.1
Osmotic pressure ratio (to physiological saline)	0.44

Product's name	Active ingredient Diltiazem hydrochloride	Vehicle D-mannitol
HERBESSER® Powder Injection (50 mg/vial)	50 mg	75 mg

(A C T I O N S)

Pharmacological studies :

This product exerts vasodilating action and slows atrioventricular nodal conduction by inhibiting calcium channel influx to cells in vascular smooth muscles such as peripheral vessels, coronary vessels, etc. and atrioventricular node, and shows the efficacy for hypertension, arrhythmia, and angina pectoris.

1. **Action on blood pressure**
   1) It decreases high blood pressure under anesthetized and unanesthetized conditions. The antihypertensive effect is more potent under anesthetized condition than under unanesthetized conditions. [7)] In addition, it exerts stronger antihypertensive action on higher blood pressure than on normal levels (rats). [8,9)]
   2) It reduces peripheral vascular resistance and myocardial oxygen consumption due to decreased blood pressure, and increases cardiac output (dogs). [10)]
   3) It does not reduce blood flow in the brain, coronary vessels, and kidney, while decreases blood pressure. It also exerts natriuretic action (dogs and monkeys). [10-12)]

2. **Action on arrhythmia**
   1) It slows conduction, effective refractory period, and functional refractory period of the atrioventricular node, and exerts effects on supraventricular tachyarrhytmia (dogs). [13)]
   2) It inhibits supraventricular tachyarrhytmia induced by atrial electric stimulation (rabbits). [14)]

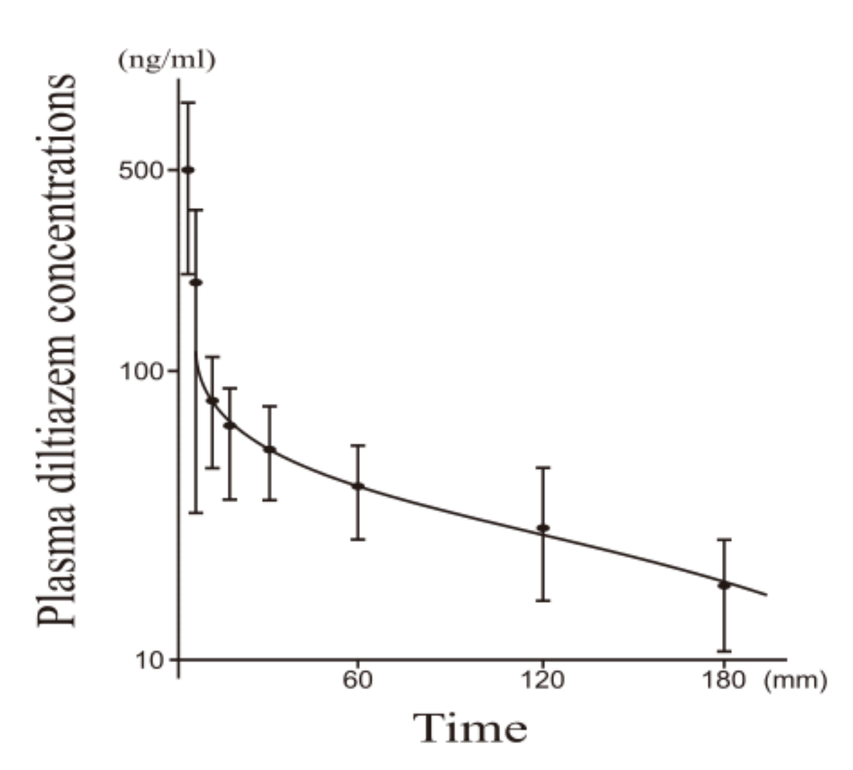
3. **Action on myocardial ischemia.**
   1) Improvement of myocardial oxygen demand and supply balance
      (1) It dilates large coronary vessels and collateral channels, and increases blood flow to myocardial ischaemic lesions (dogs). [12,15-17)]
      (2) It inhibits coronary artery spasm (pigs and humans). [18,19]
   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 (dogs and cats). [20,21)]

PHARMACOKINETICS :

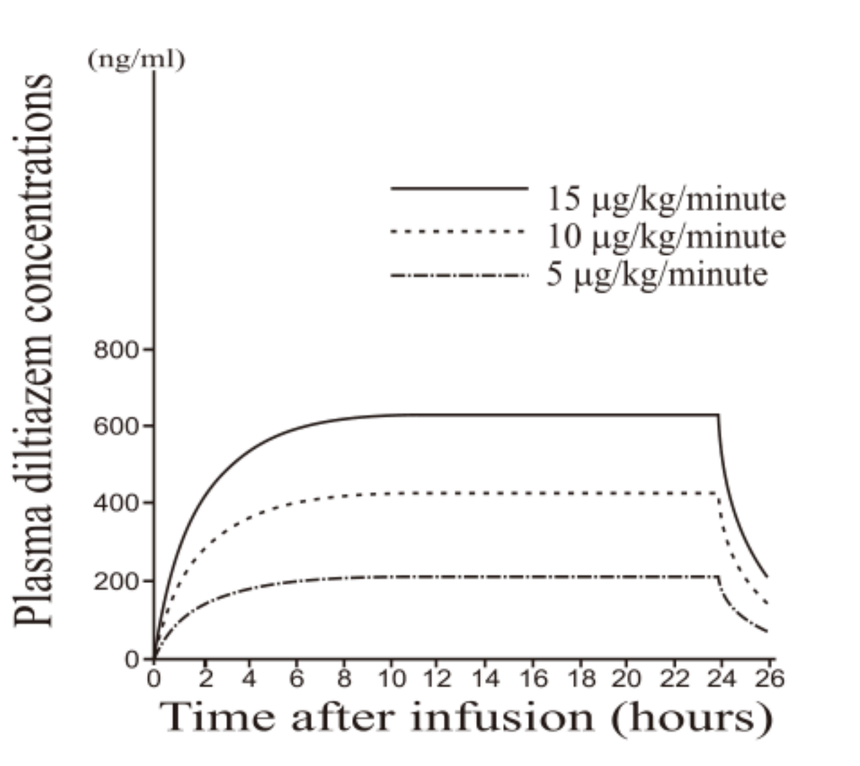
Plasma concentration

An elimination half-life (elimination phase) of diltiazem after single intravenous administration was about 1.9 hours. The plasma concentration reached a steady state within 5 to 6 hours after intravenous infusion.

Intravenous administration [1)]
8 patients with cardiac diseases
10 mg of diltiazem hydrochloride administered intravenously over one minute



Intravenous infusion [2)]
Simulation curve calculated based on actual measured values when 5, 10 or 15 µg/kg/minute of diltiazem hydrochloride was administered to 5 patients who had not received open-heart surgery



CLINICAL STUDIES

1. **Tachyarrhythmia (Supraventricular)**
   Clinical studies including a placebo-controlled, double-blind comparative study have shown the usefulness of HERBESSER® Powder Injection for paroxysmal supraventricular tachycardia, tachycardiac atrial fibrillation, and tachycardiac atrial flutter. The efficacy rate (more than effective) was 86.4% (184/213) in paroxysmal supraventricular tachycardia, and 87.2% (130/149) in tachycardiac atrial fibrillation, and tachycardiac atrial flutter.

2. **Emergency treatment for abnormal hypertension during operation**
   Clinical studies including a single blind comparative study using nitroglycerin (injection) as a control[4)] have shown the usefulness of this product for emergency treatment of abnormal hypertension during operation. The efficacy rate (more than effective) was 94.0% (315/335).

3. **Hypertensive emergency**
   The efficacy rate (more than effective) was 100.0% (28/28) for hypersensitive emergency such as malignant hypertension, hypersensitive encephalopathy, dissecting aortic aneurysm, acute left cardiac failure, etc. [5)]

4. **Unstable angina**
   A randomized single blind comparative study [6)] has shown the usefulness of this product for unstable angina. The efficacy rate (more than moderate improvement) was 80.0% (32/40).

(INDICATIONS)

- Tachyarrhythmia (supraventricular).
- Emergency treatment for abnormal hypertension during operation.
- Hypertensive emergency.
- Unstable angina.

(DOSAGE AND ADMINISTRATION)

HERBESSER® Powder Injection (50 mg as Diltiazem hydrochloride) is dissolved in at least 5 ml of physiological saline or glucose solution for injection before use, and administered as follows :

- Tachyarrhythmia (supraventricular)
  Usually for adults, 10 mg of Diltiazem hydrochloride as a single dosage is intravenously injected slowly over about 3 minutes. The dosage may be adjusted depending on the patient's age and symptoms.

- Emergency treatment for abnormal hypertension during operation.
  Intravenous bolus injection :
  Usually for adults, 10 mg of Diltiazem hydrochloride as a single dosage is intravenously injected slowly over about one minute. The dosage may be adjusted depending on the patient's age and symptoms.
  Intravenous drip infusion :
  Usually for adults, intravenous drip infusion is started at a rate of 5 to 15 µg Diltiazem hydrochloride/kg body weight per minute. After blood pressure is decreased to the target level, adjust the drip infusion rate while monitoring blood pressure.

- Hypertensive emergency.
  Usually for adults, intravenous drip infusion is started at a rate 5 to 15 µg Diltiazem hydrochloride/kg body weight per minute. After blood pressure is decreased to the target level, adjust the drip infusion rate while monitoring blood pressure.

- Unstable angina
  Usually for adults, intravenous drip infusion is started at a rate 1 to 5 µg Diltiazem hydrochloride/kg body weight per minute. The dosage should be started low, and it may be adjusted depending on the patient's symptoms. The maximum dosage should be 5 µg Diltiazem hydrochloride/kg body weight per minute.

(CONTRAINDICATION)

HERBESSER® Powder Injection is contraindicated in the following patients

1) Patients with severe hypotension or cardiogenic shock [These symptoms 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 severe congestive cardiac failure [Symptoms of cardiac failure may be aggravated.]
4) Patients with severe cardiomyopathy [Symptoms of cardiac failure may be aggravated.]
5) Patients with a history of hypersensitivity to any of the ingredients of this drug.
6) Pregnant women or women who may possibly be pregnant, etc. [See "Use during Pregnancy, Delivery or Lactation" section.]

(PRECAUTIONS)

1. **Carefully administration (HERBESSER® Powder Injection 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 cardiomyopathy [Symptoms of cardiac failure maybe aggravated.]
   3) Patients with acute myocardial infarction [Symptoms of cardiac failure maybe aggravated.]
   4) Patients with bradycardia or first degree atrioventricular block [Depression of cardiac stimulation and cardiac conduction may occur excessively.]
   5) Patients with hypotension [Blood pressure may be further decreased.]
   6) Patients with atrial fibrillation or atrial flutter associated with WPW or LGL syndromes [Increased heart rate or venticular fibrillation associated with hypotension may occur.]
   7) Patients being treated with beta blocker [Bradycardia or depression of cardiac conduction may occur excessively.]
   8) 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) Electrocardiogram and blood pressure should be monitored continuously.
   2) Since complete atrioventricular block, severe bradycardia may occur, possibly leading to cardiac arrest, adequate attention should be taken to the following points. [See "Adverse Reactions" section.]
      (1) The patients should be treated with minimum dosage for treatment. In case of intravenous infusion, the dosing should be limited to the minimum duration of time.
      (2) The patients should be observed carefully during and after the administration for early detection of these symptoms.
      (3) Prior to administration, adequate preparations should be maid to treat these symptoms. If any abnormalities are observed, administration should be discontinued immediately, and appropriate therapeutic measures should be taken.
   3) Prolonged QT and ventricular arrhythmia including torsades de pointes have been reported in co-administration of terfenadine with other antiarrhythmic agents (disopyramide phosphate)
   4) In case of severe angina attack such as persisting for more than 15 minutes, other treatments (such as PTCA, CABG, etc.) should be considered as needed.

3. **Adverse Reaction**
   Adverse reactions were reported in 266 (4.1%) of 6,543 patients tested. The major adverse reactions were bradycardia (1.1%), decreased blood pressure (0.7%), first degree atrioventricular block (0.4%), second degree atrioventricular block (0.3%), atrioventricular junctional rhythm (0.3%), etc. (at the time of latest reexamination)

   1) **Clinically significant adverse reactions** (occasionally: 5%>-≥0.1%, rarely: <0.1%)
      1) **Complete atrioventricular block, severe bradycardia** (early symptom: bradycardia, dizziness, lightheadedness, etc.) may occasionally occur, possibly leading to cardiac arrest. Therefore, adequate preparations should be maid to treat these symptoms prior to administration. If these abnormalities are observed, administration should be discontinued at once, and the following appropriate therapeutic measures should be taken. Complete atrioventricular block, severe bradycardia: Atropine sulfate hydrate, isoprenaline, etc. should be administered or appropriate therapeutic measures such as cardiac pacing should be taken as needed. Cardiac arrest: Resuscitate measures such as cardiac massage, administration of catecholamine such as adrenaline, etc. should be taken.

Belakang / *back*

      2) **Congestive heart failure** may occur rarely. If any signs of congestive cardiac failure 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 unknown	5% > - ≥ 0.1%	< 0.1%
Cardiovascular	-----	Bradycardia, atrioventricular block, decreased blood pressure, atrioventricular junctional rhythm, extra systoles, sinus arrest, facial flushing	Sinoatrial block, bundle branch block, palpitation, dizziness, transient tachycardia
Psychoneurotic	-----	-----	Headache, nausea, vomiting.
Hepatic	-----	Increased AST (GOT), increase ALT (GPT), increased LDH.	Increased A1-P
Renal	-----	-----	Decreased urine volume, increased serum creatinine, increased BUN
Hypersensitivity	Photosensitivity*	-----	Rash, pruritus
Other	Phlebitis	-----	Local injection site redness

* Case reports of oral preparation of this product

4. **Use in the Elderly**
   Since elderly patients often have reduced physiological function, HERBESSER® Powder Injection should be administered with care such as starting from lower dosage while carefully monitoring patient's condition

5. **Use during Pregnancy, Delivery or Lactation**
   1) HERBESSER® Powder Injection is contraindicated in pregnant women or women who may possibly be pregnant. [Animal studies have shown that the drug has teratogenic effects (mice, rats, rabbits, skeletal abnormalities, dysplasias) and embryotoxicity (mice, rats, rabbits, death).
   2) Use of this product in lactating women is not recommended. If treatment with this product is judged to be essensial, breast feeding must be discontinued during treatment. [It has been reported that diltiazem is excreted in human breast milk.]

6. **Pediatric Use**
   The safety of HERBESSER® Powder Injection in children has not been established.

7. **Over dosage**
   Symptoms :
   Bradycardia, complete atrioventricular block, cardiac failure, hypotension, etc. may occur after overdosage of HERBESSER® Powder Injection. These symptoms have been also reported as adverse reactions.

   Treatment :
   In case of overdosage, administration should be discontinued, 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 :
      Administer intravenous fluids, an inotropic agent, a pressor agent , etc. should be administered or assisted circulation should be performed.

8. **Drug Interactions**
   This product is metabolized mainly by cytochrome P450 3A4 (CYP3A4) metabolizing enzyme.
   Precautions for co-administration (HERBESSER® Powder Injection should be administered with care when co-administered with the following drugs.)

Drugs	Signs, Symptoms & Treatment	Mechanism & Risk Factors
Drugs with antihypertensive effects (Antihypertensive drugs, nitric acid preparations, etc.)	Antihypertensive effects may be intensified. Blood pressure should be measured to adjust the dosage	Antihypertensive effects may be intensified additively
Beta-blockers (bisoprolol fumarate, propanolol hydrochloride, atenolol, etc.) Rauwolfia preparations (reserpine, etc.)	Bradycardia, atrioventricular block, sinoatrial block, 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, 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, metildigoxin)	Bradycardia, atrioventricular block, etc. may occur. In addition, toxic symptoms (nausea, vomiting, headache, dizziness, abnormal vision, etc.) including the above arrhythmic symptoms may occur due to increased blood concentration of digitalis preparation. Electrocardiogram should be monitored. In addition, presence or absence of digitalis toxicity should be observed periodically, and 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 increase blood concentrations of digitalis preparations.
Antiarrhythmic agents (amiodarone hydrochloride, mexiletine hydrochloride, 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.
Aprindine hydrochloride [antiarrythmic agents]	Symptoms (bradycardia, atrioventricular block, sinus arrest, tremor, dizziness, lightheadedness, etc.) may occur due to increased blood concentrations of both drugs. Electrocardiogram should be monitored. In addition, clinical symptoms should be observed periodically. If any abnormalities are observed, the dosage should be reduced or administration should be discontinued.	Each drug may affect a common metabolizing enzyme (cytochrome P450), and increase blood concentration of each drug.
Dihydropyridine calcium antagonist (nifedipine, amlodipine besilate, etc.)	Symptoms (intensified antihypertensive effects, etc.) may occur due to increased blood concentration of dihydropyridin 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.
Triazolam [hypnotic agent]	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 [hypnotic sedative agent]	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.	
Carbamazepine [psychotoropicantiepileptic agent, antimanic agent]	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.	This product may inhibit the metabolizing enzyme (cytochrome P450) of these drugs, and increase their blood concentrations.
Selegiline hydrochloride [antiparkinson agent]	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 [bronchodilator]	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 [antiplatelet agent]	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 [anticancer drug]	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.	
Ciclosporin [immunosuppressant]	Symptoms (renal disorder, etc.) may occur due to increased blood concentration of ciclosporin. 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.	
Tacrolimus hydrate [immunosuppressant]	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.	
Phenitoin [antiepleptic drug]	Symptoms (ataxia, dizziness, nystagmus, etc.) may occur due to increased blood concentration of phenitoin. 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 phenitoin, and increase blood concentration of phenitoin. In addition, phenitoin may stimulate metabolism of this product, and decrease blood concentration of this product.
Cimetidine [H2 receptor antagonist] HIV protease inhibitors (ritonavir, saquinavir mesylate, etc.)	Symptoms (intensified antihypertensive effect, bradycardia, etc.) may occur due to increased blood concentration of this product. Blood pressure should be measured, and electrocardiogram should be monitored. 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 drug, and increase blood concentration of this product.
Rifampicin [antituberculous drug]	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.
Anesthetic 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 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 the presynaptic terminals at the neuromuscular junction

9. **Precautions concerning use**
   Precautions in Preparation :
   Caution should be excercised in case where pH exceeds 8 due to combination with other drugs, diltiazem precipitation may occur.

(HANDLING)

Caution	:	Use only pursuant to the prescription or directions of a physician.
Storage	:	Store at below 30°C, away from direct light.
Expiration date	:	Indicated on the package and container
Shelf life	:	36 months

(PRESENTATION)

HERBESSER® Powder Injection 50 mg
Box of 50 mg x 10 vials Reg. No. DKI1334200144B1

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ON DOCTOR'S PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

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Osaka, Japan

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