$Ca^{++}$-Antagonist

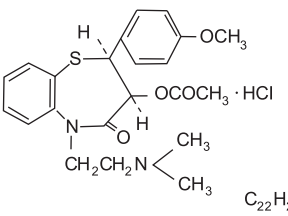
# HERBESSER® 90 SR

Reg. No. DKL9025200603A1

## ( COMPOSITION AND DESCRIPTION )

Physicochemical properties of active ingredient

- INN (name in J.P.) : Diltiazem hydrochloride
- Chemical name : d–3–Acetoxy–cis–2,3–dihydro–5–[2–( dimethylamino ) ethyl ] –2–( p–methoxyphenyl )–1,5– benzothiazepin – 4 ( 5H) – one hydrochloride



$C_{22}H_{26}N_2O_4S.HCl$ : 450.99

- 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, slighty soluble in dehydrated ethanol and in acetic anhydride, and practically insoluble in ether.
– Melting point : 210°- 215° C (decomposition )

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

## ( ACTIONS )

### ( PHARMACOLOGICAL STUDIES )

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

1. Action on blood pressure
   (1) Lowers the elevated blood pressure gradually although hardly affects the normal blood pressure (rat, human).[1 ~ 3]
   Suppresses the elevation of blood pressure induced by exercise load ( human ).[4]
   (2) Lowers blood pressure without decreasing cerebral and renal blood flow ( dog, human ).[5 ~ 8]
   (3) Suppresses myocardial and vascular hypertrophy together with lowering blood pressure ( rat ).[9]
2. Effects on myocardial ischemia
   (1) Increases coronary blood flow into myocardial ischemic region by dilating the collateral channels and large coronary artery ( dog ).[10 ~ 13]
   (2) Suppresses coronary artery spasms (monkey, human ).[14, 15]
   (3) Decreases myocardial oxygen consumption without decreasing cardiac output by decreasing after-load and heart rate due to peripheral vasodilating effect ( dog ).[16]
   (4) Retains cardiac function and myocardial energy metabolism and reduces the infarct size by inhibiting extra calcium ion influx during myocardial ischemia ( rat ).[17]
3. Action on sinus rhythm and cardiac conduction system.
   Slightly prolongs spontaneous sinus rhythm interval and A - V node conduction time. Does not affect on His - Purkinje conduction time ( dog, human ).[16, 18, 19]

### ( PHARMACOKINETICS )

1. Plasma level
   When 1 capsule (90 mg as diltiazem hydrochloride) of HERBESSER® 90 SR was orally administered to healthy adult men, its plasma level reached the peak (about 40 ng/ml) about 7 hours after administration.[20]
   The plasma elimination half life was about 8.4 hours. In case of repeated administration of HERBESSER® 90 SR twice a day to healthy adult men, plasma level at 1 to 10 hours after administration was about 91 ng / ml.[21]
2. Metabolism
   When HERBESSER® 90 SR was administered to healthy adult men, deacetyl diltiazem, deacetyl - N - monodemethyl diltiazem, deacetyl - 0 - demethyl diltiazem, deacetyl - N, 0 - demethyl diltiazem and N - monodemethyl diltiazem were detected in urine as metabolites. A part of these metabolites are conjugated with glucuronic acid or sulfuric acid in body.[22]

### ( CLINICAL STUDIES )

1. Hypertension
   Usefulness of HERBESSER® 90 SR in the treatment of essential hypertension was proved by four double - blind comparative studies with placebo, reserpine and propranolol as control drugs.[23 ~ 26]
2. Angina pectoris
   Usefulness of HERBESSER® 90 SR in the treatment of anginal pain due to effort angina and old myocardial infarction was proved by two double - blind comparative studies including a placebo - controlled study.[27, 28]
3. Adverse reactions
   432 cases (4.5%) of adverse reactions were reported out of total 9,347 cases. The most common occurences as well as their frequency of presentation are : Gastrointestinal system 1.3% (stomach discomfort 0.2%, constipation 0.2%, abdominal pain 0.1%, etc), cardiovascular system 1.3% (bradycardia 0.4%, dizziness 0.4%, hot flush of face 0.2%, A - V block 0.2%, etc.) hypersensitivity 1.2%, headache 0.2%,. etc.

### ( PRECLINICAL STUDIES )

1. Toxicity

   (1) Acute toxicity ($LD_{50}$ mg /kg )[29]

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

   (2) Chronic toxicity

   When 2, 10 and 25 mg/kg/day each of diltiazem hydrochloride were given orally to SD - strain rats and 5, 10 and 20 mg/kg/day to beagle dogs, for successive six months respectively, general state as well as urinary and histopathological findings of these animals were not significantly different from those of the control. Hematological findings in dogs given orally 20 mg/kg of diltiazem hydrochloride revealed a rise of GPT but it was transient and tended to recover the normal level at the end of experiment.[30]

15-6-21 15-6-21

DISETUJUI OLEH BPOM: 01/03/2023 ID REG: EREG10002812300029

2. Teratogenecity
The effect of diltiazem hydrochloride on the fetus was examined by the method as specified in " Policy for Assurance of Drug Safety " notified by the Ministry of Health and Welfare of Japan. At the oral dose level of more than 10 mg / kg in ICR - JCL - strain mice and more than 200 mg / kg in Wistar - strain rats, diltiazem hydrochloride caused death of the fetus. At the oral dose level of more than 50 mg / kg in ICR - JCL - strain mice, diltiazem hydrochloride provoked teratogenic effect. At an oral dose of 400 mg / kg in Wistar - strain rats, diltiazem hydrochloride did not provoke teratogenic effect.[31]

## ( INDICATION )

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

## ( DOSAGE AND ADMINISTRATION )

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

## ( PRECAUTIONS )

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

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

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

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

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

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

7. Drug interaction :
HERBESSER® 90 SR should be carefully administered in case of concomitant use with the following drugs :
   (1) Antihypertensive agents ( effect of antihypertensive agents is enhanced ).
   (2) Beta - blocking agents or rauwolfia preparations ( bradycardia may occur ).
   (3) Carbamazepine ( plasma level of carbamazepine may be increased and it may cause carbamazepine-induced toxic symptoms such as sleepiness, nausea, vomiting, vertigo, etc. )
   (4) Digoxin preparations ( plasma level of digoxin is increased ).
   (5) Cimetidine ( peak plasma level of diltiazem and area under the curve may be increased ).
   (6) The depression of cardiac contractility, conductivity and automaticity, as well as the vascular dilation associated with anesthetics may be potentiated by calcium antagonists. When used concomitantly, anesthetics and calcium antagonists should be titrated carefully.

## ( HANDLING )

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

Storage : Store in a tight and light-resistant container at below 30° C.
Shelf Life: 3 years

## ( PRESENTATION )

- Box of 10 blister sheets of 10 capsules

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References are available on request

**ON DOCTOR'S PRESCRIPTION ONLY**
**HARUS DENGAN RESEP DOKTER**

Under license from
Mitsubishi Tanabe Pharma Corporation
Osaka, Japan

Manufactured by
PT Mitsubishi Tanabe Pharma Indonesia
Bandung, Indonesia

15-6-21 15-6-21

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