- HYPOTENSIVE DRUG -

BEHYD-RA® Combination Tablets

Prescription drug

**Storage**

This product should be stored in a light-proof container at room temperature.

**Expiration date**

This product should be used before the expiration date indicated on the outer cases and containers.

<table>
<thead>
<tr>
<th>Approval No.</th>
<th>22100AMX01200000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>September 2009</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>August 1961</td>
</tr>
<tr>
<td>Date of latest reevaluation</td>
<td>August 1980</td>
</tr>
</tbody>
</table>

Note) Caution: Use only as directed by a physician.

**WARNINGS**

Serious depression may occur. Read the section of the “PRECAUTIONS” carefully, before use of this product.

**CONTRAINDICATIONS (This product is contraindicated in the following patients.)**

1. Patients with anuria
   
   [This product is ineffective for patients with anuria. Administration of this product may induce azotemia.]

2. Patients with acute renal failure
   
   [This product is ineffective for patients with acute renal failure. Administration of this product may induce azotemia.]

3. Patients with marked decreases in sodium and potassium of the body fluid.
   
   [Since this product discharges sodium and potassium, administration of this product may further decrease their concentrations in the body fluid resulting in exacerbation of electrolyte imbalance.]

4. Patients with depression/depressive symptoms or their histories, especially those with suicidality
   
   [Ataractic action of reserpine, an ingredient in this product, may exacerbate the symptoms.]

5. Patients with peptic ulcer or ulcerative colitis
   
   [Since reserpine contained in this product has inhibitory action on the sympathetic nervous system, administration of this product may increase the peristaltic movement of the gastrointestinal tract through predominant activity of the parasympathetic nervous system to enhance secretion of gastric acid, resulting in exacerbation of the symptoms.]

6. Patients with a history of hypersensitivity to thiazide drugs or their related substances (e.g., sulfonamide derivatives such as chlorthalidone), rauwolfia alkaloids, or carbasochrome

7. Patients undergoing electric shock therapy
   
   [Concomitant use of this product with electric shock therapy may induce a serious reaction.] (See the section of “Drug Interactions.”)

8. Patients during treatment with tetrabenazine (See the section of “Drug Interactions.”)

9. Women during pregnancy or lactation (See the section of “Use during Pregnancy, Delivery or Lactation.”)

10. Patients during treatment with terfenadine or astemizole
    
    [Prolonged QT and ventricular arrhythmia may occur. Separately, concomitant use of other diuretic (a loop diuretic) with terfenadine has been reported to induce prolonged QT and ventricular arrhythmia.]

**DESCRIPTION**

**Product description**

- Benzylhydrochlorothiazide 4 mg
- JP reserpine 0.1 mg
- Carbasochrome 5 mg
- Lactose hydrate, potato starch, magnesium stearate
- Plain
- Reddish orange
- 7.0 mm in diameter
- 2.7 mm in thickness
- About 120 mg in weight
- KP-085

**INDICATIONS**

Hypertension (essential, renal, etc.), malignant hypertension

**DOSAGE AND ADMINISTRATION**

The usual adult dosage of this product for oral use is 1 or 2 tablets once or twice daily. If blood pressure reduces to reach a plateau, 1 or 2 tablets of this product are orally administered as a daily maintenance dose.

The dosage may be adjusted according to the patients’ ages and symptoms.

**PRECAUTIONS**

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

   (1) Patients with advanced hepatic cirrhosis
       [Administration of this product may induce hepatic coma.]
(2) Elderly patients with heart disease, and patients with serious coronary or cerebral arteriosclerosis
[Acute diuresis may induce a rapid decrease in the amount of plasma with hemoconcentration, potentially resulting in development of thromboembolism.]

(3) Patients with serious nephropathy
[Administration of this product may induce azotemia. In addition, patients with renal dysfunction may induce deterioration in adaptability to reduction in blood pressure.]

(4) Patients with hepatic disease or dysfunction
[Administration of this product may further exacerbate hepatic function.]

(5) Patients with gout or diabetes mellitus, or those with family histories of these diseases
[Since this product may increase the levels of urate and glucose in the blood, administration of this product may induce or further exacerbate gout or diabetes.]

(6) Patients with diarrhea or vomiting
[Administration of this product may induce electrolyte imbalance.]

(7) Patients with hypercalcemia or hyperparathyroidism
[Administration of this product may exacerbate hypercalcemia.]

(8) Patients undergoing treatment with a digitalis preparation, glucocorticoid, or ACTH (See the section of “Drug Interactions.”)

(9) Patients undergoing hypochloric therapy
[Administration of this product may induce hyponatremia.]

(10) Elderly patients (See the section of “Use in the Elderly.”)

(11) Infant patients (See the section of “Pediatric Use.”)

Articles (3) to (11) should be referred to the section of “Clinically Significant Adverse Reactions” and the heading of “Metabolic abnormality” in the section of “Other Adverse Reactions.”

2. Important Precautions

(1) As a rule, this product should be used only when a monotherapy is insufficient for obtaining hypotensive response.

(2) Since diuretic action of this product may steeply occur, attention should be paid to electrolyte imbalance or dehydration, with the start of a low dose and gradual increases in the dose thereafter.

(3) Since repeated doses of this product may induce electrolyte imbalance, patients should be monitored with the regular examinations.

(4) For patients in whom a sufficient nocturnal sleep is essential, administration in the morning is recommended to avoid nocturnal urination.

(5) Since administration of this product may induce dizziness or stagger resulting from its hypotensive action, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machines, working in heights, and driving cars.

3. Drug Interactions

(1) Contraindications for coadministration (This product should not be coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electric shock therapy</td>
<td>Serious reactions (confusion, lethargy, severe hypotension, etc.) may occur.</td>
<td>Reserpine is considered to reduce the thresholds of convulsions</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>This product and tetrabenazine may enhance actions synergistically.</td>
<td>Tetrabenazine has similar mechanism of action of this product.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetrabenazine may enhance the effect of this product.</td>
</tr>
</tbody>
</table>

(2) Precautions for coadministration (This product should be administered with care when coadministered with the following drugs)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates</td>
<td>All these drugs may enhance orthostatic hypotension.</td>
<td>CNS depressant actions of these drugs and hypotensive action of the diuretic induce the symptom.</td>
</tr>
<tr>
<td>Opioid alkaloids</td>
<td></td>
<td>Megadose of an opioid alkaloid has been reported to induce hypotension.</td>
</tr>
</tbody>
</table>
### Alcohol

Coadministration of this product with alcohol with vasodilation may enhance the hypotensive action.

These drugs have been reported to decrease the responsiveness of the vascular walls, and release of physiological noradrenaline from the sympathetic terminal.

### Catecholamines: Noradrenaline Adrenaline

Coadministration may attenuate the actions of catecholamines. If any of these drugs is used in preoperative patients, a washout period for this product should be set.

These drugs have been reported to decrease the responsive ness of the vascular walls, and release of physiological noradrenaline from the sympathetic terminal.

### Tubocurarine and its related substances: Tubocurarine chloride Pancuronium bromide Vecuronium bromide

Coadministration may enhance the paralyzing actions of these drugs. If any of these drugs is used in preoperative patients, a washout period for this product should be set.

Neuromuscular blockade actions of these drugs are possibly increased by a decrease in serum potassium due to the diuretic.

### Other hypotensive drugs: ACE inhibitors β-Blockers Nitroglycerine, etc.

Coadministration may enhance the hypotensive action, and the adverse reactions of reserpine and β-blockers, resulting in development of bradycardia and excessive sedation. Attention should be paid to appropriate measures, such as adjusted dosages of hypotensive drugs.

Synergic action is made with hypotensive drugs with different mechanisms. An excess inhibitory action on the sympathetic system may be induced with β-blockers and reserpine, because reserpine depletes catecholamines.

### Digitalis products: Digoxin, etc.

Coadministration may enhance the effect of digitalis on the heart, resulting in development of arrhythmia. Attention should be paid to the levels of serum potassium.

Binding of digitalis to myocardial Na-K ATPase is facilitated by a decrease in serum potassium due to the diuretic, resulting in enhancement of cardiac contractility and development of arrhythmia. Similar action occurs through a decrease in serum magnesium. These actions are also probably involved in a catecholamine release in the sympathetic terminal by reserpine.

### Quinidine

Bradycardia may occur.

Coadministration may alkalify the urine to increase the level of non-dissociative quinidine, leading to an increase in the plasma concentration of quinidine.

### Glucocorticoids: ACTH Glycyrrhizin products

Hypokalemia may occur.

Both drugs have potassium-eliminating actions.

### Therapeutic drugs for diabetes: SU products Insulin, etc.

Since coadministration may exacerbate diabetes (or reduce the action of an antidiabetic drug), attention should be paid.

Decrease in the level of potassium due to the diuretic may reduce insulin release from the β cells in the pancreas, although the mechanism remains unclear.

### Lithium carbonate

Since coadministration may enhance lithium poisoning symptoms such as tremor and dyspepsia, attention should be paid to the serum concentrations of lithium.

The diuretic accelerates reabsorption of lithium in the kidneys to increase the blood concentrations of lithium.

### Cholestyramine

Diuretic hypotensive actions are reduced.

Adsorbent action of cholestyramine inhibits absorption of this product.

### Nonsteroidal antiinflammatory analgesics: Indomethacin, etc.

Inhibitory effects of nonsteroidal anti-inflammatory analgesics on prostaglandin synthase decrease the levels of prostaglandins in the kidneys to accumulate water and sodium in the body fluid, which antagonizes the action of this product.

### Dopamine agonists: L-dopa Droxidopa, etc.

Coadministration may attenuate the effects of dopamine agonists.

Reserpine may decrease the level of dopamine in the brain, and antagonize the anti-parkinsonian effects of dopamine agonists.

### Antidepressants

Coadministration may attenuate the effects of antidepressants.

Antidepressants may increase the concentrations of amines in
antidepressants and hypotensive effect of reserpine, and induce excess analeptic action.

The synaptic cleft by mainly inhibiting re-uptake of catecholamines and serotonin.

**MAO inhibitors**

Administration of reserpine to patients taking MAO inhibitors may induce excitation and increased blood pressure.

Reserpine may enhance the responsiveness of catecholamines through their increased release, when coadministered after MAO inhibitors increased accumulation of catecholamines.

**Sympatholytics:**

Guanethidine
Bethanidine, etc.

Coadministration may induce bradycardia, orthostatic hypotension and depression.

This product and sympatholytics may enhance catecholamine-depleting actions synergistically.

**Anticholinergic antiparkinson drugs:**

Trihexyphenidyl, etc.

Reserpine may enhance the effects of anticholinergic antiparkinson drugs.

This product and anticholinergic antiparkinson drugs may enhance CNS-depressant actions synergistically.

4. **Adverse Reactions**

This product has not been investigated (Drug-use results surveys, etc.) to determine the incidence of adverse reactions. The incidence data on this product have therefore been collected from the literature and spontaneous reports. Out of a total of 522 cases, 30 cases (5.7%) had adverse reactions (the results of reevaluation).

Adverse reactions with their incidences unknown are also included in the following data:

(1) **Clinically Significant Adverse Reactions**

**1) Depression** (0.2%)

Since serious depression leading to suicide may occur, special attention should be paid to the patients’ conditions. Administration should be discontinued if depressive symptoms such as depressed state, early morning awakening, anorexia, and impotence or suppression (thinking and behavior) are observed. Such symptoms may persist for several months even after discontinuation of administration.

**2) Aplastic anemia** (incidence unknown)

Since aplastic anemia may occur, the patients should be carefully monitored. If any of abnormal findings is observed, administration should be discontinued.

**3) Hyponatremia** (incidence unknown)

Since hyponatremia with malaise, anorexia, nausea, vomiting, convulsion and/or disturbed consciousness may occur, the patients should be carefully monitored. If any of abnormal findings is observed, appropriate measures such as suspension of administration should be taken immediately.

**4) Hypokalemia** (0.1≤ <5%)

Since hypokalemia with malaise, weakness and/or arrhythmia may occur, the patients should be carefully monitored. If any of abnormal findings is observed, appropriate measures such as suspension of administration should be taken immediately.

(2) **Clinically Significant Adverse Reactions (Related Drugs)**

**Interstitial pneumonia and pulmonary edema**

Since administration of a related drug (hydrochlorothiazide) has been reported to induce interstitial pneumonia or pulmonary edema, the patients should be carefully monitored. If any of abnormal findings is observed, administration should be discontinued.\(^1\)

**3) Other Adverse Reactions**

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>0.1≤ &lt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoneurologic (Note1)</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Nightmare(^{\text{Note2}}), extrapyramidal symptom, sleepiness, decreased libido, nervousness, headache, general tremor, paresthesia, etc.</td>
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</tbody>
</table>

| Hematologic\(^{\text{Note3}}\) | Hemopathies such as leukopenia, thrombocytopenia, and purpura |

<table>
<thead>
<tr>
<th>Hepatic</th>
<th>Hepatitis</th>
</tr>
</thead>
</table>

| Metabolic abnormality \(^{\text{Note4}}\) | Electrolyte imbalances, such as hypomagnesemia, hypochloremic alkalosis, and increased serum calcium, an increase in serum lipids, hyperuricemia, hyperglycemia |

<table>
<thead>
<tr>
<th>Sensitivity (^{\text{Note5}})</th>
<th>Photo-sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, facial flushing, etc.</td>
<td></td>
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</tbody>
</table>

| Gastrointestinal | Gastric ulcer, vomiting, stomach discomfort, pancreatitis, sialoadenitis, etc. |
| Thirst, diarrhea, loose stool, anorexia, nausea, constipation |

| Ophthalmic | Abnormal vision (blurred vision), xanthopsia, etc. |
| Abnormal vision |

| Others | Nasal obstruction |
| Malaise, impotence, exacerbation of systemic lupus erythematosus, body weight gain, muscle spasm, dyspnea |

Note1: The patients should be carefully monitored. If any abnormality is observed, appropriate measures such as a reduced dosage or suspension of administration should be taken.

Note2: In the case of megadose or long-term administration.
Note3): The patients should be carefully monitored. If any abnormality is observed, administration should be discontinued.
Note4): The patients should be monitored with regular examinations. If any abnormality is observed, appropriate measures such as a reduced dosage or suspension of administration should be taken.

5. Use in the Elderly
This product should be carefully administered to elderly patients with appropriate measures including the low starting dose, while the patients' conditions are closely monitored, paying attention to the following points.
1) In elderly patients, rapid diuresis may induce a decrease in plasma amount to cause orthostatic dizziness, dizziness and syncope due to dehydration or hypotension.
2) In particular, in the elderly patients with edema resulting from heart disease, rapid diuresis may cause a steep decrease in plasma amount and hemoconcentration to induce thromboembolism including cerebral infarction.
3) In general, excessive hypotension is considered unfavorable in elderly patients.
   [Cerebral infarction may occur.]
4) In elderly patients, hyponatremia and hypokalemia are likely to occur.
5) In elderly patients, depression/depressive symptoms are likely to occur.

6. Use during Pregnancy, Delivery or Lactation
(1) This product should not be administered to early pregnant or possibly pregnant women.
   [An animal study in rats has demonstrated that reserpine has teratogenic effect.]
(2) This product should not be administered to late pregnant or nursing women.
   [Reserpine and benzylhydrochlorothiazide have been reported to cross the placenta and be excreted in the breast milk. Therefore, administration of this product may induce increased pulmonary secretions, nasal hyperemia, cyanosis, anorexia, hyperbilirubinemia, and thronbocytopenia in newborns. In addition, diuretic action of benzylhydrochlorothiazide may cause a decrease in plasma amount, hemoconcentration, and decreases in the blood flow of the uterus and placenta.]

7. Pediatric Use
Since infants are likely to induce electrolyte imbalance, special attention should be paid when this product is used in infants.

8. Effects on Laboratory Results
(1) Since this product may decrease serum PBI in patients without thyroid disorder, special attention should be paid to the administration.
(2) The metabolites of carbazochrome may cause positive results in the urinary urobilinogen tests.

9. Precautions Concerning Use
Precautions regarding dispensing: For the drug that is dispensed in a press-through package (PTP), patients should be instructed to remove the drug from the package prior to use. [It has been reported that if the PTP sheet is swallowed, its sharp corners may puncture the esophageal mucosa, resulting in serious complications such as mediastinitis.]

10. Other Precautions
(1) Although the causality of use of rauwolfia alkaloids including reserpine with development of breast cancer has not been established, an epidemiological study in women with breast cancer has shown that the prescription rate of the rauwolfia alkaloids was significantly higher than that of the control.
(2) A long-term oral administration study of reserpine in rats (0.25 mg/kg/day or more for 103 weeks) showed an increase in the incidence of pheochromocytoma in the adrenal medulla in males.

CLINICAL STUDIES
Clinical Response
The clinical response was 80.2% (105/131) in the clinical study in a total of 131 cases with hypertension at six medical institutions.

PHARMACOLOGY
1. Effect of Benzylhydrochlorothiazide
   Benzylhydrochlorothiazide at a dose of 10 mg/kg decreased blood pressure by 10% or more in hypertensive rats. The effect appeared at 1 hour after dosing, and persisted for at least 5 hours. In addition, benzylhydrochlorothiazide at doses of 1 mg/kg or more induced increases in excretions of Na⁺, Cl⁻, and water in rats.

2. Effect of Reserpine
   It has been reported that reserpine acts on the hypothalamus to suppress sympathicotonia resulting in vasodilation, and decreases catecholamines in the peripheral sympathetic nerves to inhibit neurotransmission resulting in a reduction in blood pressure.

3. Reasons of Combination
   (1) Hypotensive effects in the concomitant use of reserpine and benzylhydrochlorothiazide were more potent than those added in the separate use of the respective agents (rats).
   (2) Repeated loads of stress induced gastric ulcer due to reserpine after coadministration of reserpine and benzylhydrchlorothiazide; however, further coadministration (a standard ratio of 1:40:50) of carbazochrome significantly decreased the incidence of the ulcer (rats).

PHYSICOCHEMISTRY
Benzylhydrochlorothiazide:  
Nonproprietary name: Benzylhydrochlorothiazide (JAN)  
Chemical name: 6-Chloro-7-sulfamoyl-3-benzyl-3,4-dihydro-1,2,4-benzo-thiadiazine-1,1-dioxide  
Molecular formula: C₁₄H₁₄ClN₃O₄S₂  
Molecular weight: 387.86  
Structural formula:
Melting point:
245 to 253 °C (Decomposition)

Description:
Benzylhydrochlorothiazide occurs as a white crystalline powder, without odor and taste. It is freely soluble in n-buthylamine, sparingly soluble in acetone, slightly soluble in methanol, very slightly soluble in ethanol and methyl isobutyl ketone, and practically insoluble in water. In addition, it is soluble in a sodium hydroxide solution.

Reserpine:

Nonproprietary name:
Reserpine (JAN)

Chemical name:
Methyl (3S, 16S, 17R, 18R, 20R)-11,17-dimethoxy-18-(3,4,5-trimethoxybenzoyloxy)yohimban-16-carboxylate

Molecular formula:
C_{33}H_{40}N_{2}O_{9}

Molecular weight:
608.68

Description:
Reserpine occurs as a white to pale yellow crystal or crystalline powder. It is freely soluble in acetic acid (100) and chloroform, slightly soluble in acetonitrile, very slightly soluble in ethanol (95), and practically insoluble in water and diethylether. It is changeable by light.

Carbazochrome:

Nonproprietary name:
Carbazochrome (JAN)

Chemical name:
3-Hydroxy-1-methyl-5,6-indolinedione semicarbazone

Molecular formula:
C_{10}H_{12}N_{4}O_{3}

Molecular weight:
236.23

Description:
Carbazochrome occurs as a yellowish red to red crystal or crystalline powder, with no odor and a slightly bitter taste. It is slightly soluble in glacial acetic acid, very slightly soluble in water and ethanol, and practically insoluble in acetic anhydride and anhydrous ether.

PACKAGING
BEHYD-RA Combination Tablets
100 tablets (10 tablets x 10) and 500 tablets (10 tablets x 50) in a press-through package
500 tablets in a bottle

REFERENCES
4) Irikura T. et al., The Clinical Report, 11, 1901 (1977)
6) Nishino K. et al., The Clinical Report, 12, 3023 (1978)

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Kyorin Pharmaceutical Co., Ltd. Drug Information Center
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan
TEL: 0120-409-341 (Toll-free)
9:00 to 17:30 (Monday through Friday exclusive of national holidays)

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