- ANTIHYPERTENSIVE/ANTIANGINAL AGENT (Long-acting Ca antagonist) -

**CONIEL® Tablets 2**
**CONIEL® Tablets 4**
**CONIEL® Tablets 8**

*<Benidipine hydrochloride tablets (JP)>*

Powerful drug and Prescription drug*

*Caution: Use only pursuant to the prescription of a physician, etc.*

<table>
<thead>
<tr>
<th>Storage</th>
<th>2mg Tablets</th>
<th>4mg Tablets</th>
<th>8mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval No.</td>
<td>20300AMZ00737</td>
<td>20300AMZ00738</td>
<td>20300AMZ00739</td>
</tr>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>November 1991</td>
<td>November 1991</td>
<td>November 1991</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>November 1991</td>
<td>November 1991</td>
<td>November 1991</td>
</tr>
<tr>
<td>Date of latest reexamination</td>
<td>September 2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of latest approval of indications</td>
<td>June 1994 (renal parenchymal hypertension)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>International birth date</td>
<td>October 1991</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

(1) Patients with cardiogenic shock [CONIEL may cause the aggravation of underlying symptoms.]

(2) Pregnant women or women who may possibly be pregnant [See PRECAUTIONS 6.Use during Pregnancy, Delivery or Lactation.]

**DESCRIPTION**

1. Composition

<table>
<thead>
<tr>
<th>Brand name</th>
<th>CONIEL Tablets 2</th>
<th>CONIEL Tablets 4</th>
<th>CONIEL Tablets 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredients</td>
<td>2 mg of benidipine hydrochloride (JP) in each tablet</td>
<td>4 mg of benidipine hydrochloride (JP) in each tablet</td>
<td>8 mg of benidipine hydrochloride (JP) in each tablet</td>
</tr>
</tbody>
</table>

2. Product description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>CONIEL Tablets 2</th>
<th>CONIEL Tablets 4</th>
<th>CONIEL Tablets 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>6.1</td>
<td>7.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.1</td>
<td>3.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>0.08</td>
<td>0.13</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**INDICATIONS**

Hypertension, renal parenchymal hypertension, angina pectoris.

**DOSAGE AND ADMINISTRATION**

1. Hypertension, renal parenchymal hypertension

Usually for adults, 2 to 4 mg of benidipine hydrochloride is orally administered once daily after breakfast. The dosage may be adjusted depending on the age and symptoms of the patient and can be increased up to 8 mg once daily if the effect is not satisfactory with 2 to 4 mg. In case, however, of severe hypertension, 4 to 8 mg of benidipine hydrochloride is orally administered once daily after breakfast.

2. Angina pectoris

Usually for adults, 4 mg of benidipine hydrochloride is orally administered twice daily after breakfast and supper. The dosage may be adjusted depending on the age and symptoms of the patient.

**PRECAUTIONS**

1. Careful Administration (CONIEL should be administered with care in the following patients.)
(1) Patients with excessively low blood pressure
(2) Patients with serious hepatic function disorder [CONIEL may cause aggravation of hepatic function disorder.]
(3) Elderly patients [See 5. Use in the Elderly.]

2. Important Precautions
(1) Aggravation of symptoms has been reported with abrupt discontinuance of calcium antagonists. In case suspension of the administration of CONIEL is required, the dosage should be reduced gradually under close observation of the patient. Additionally, patients should be cautioned against discontinuance of the administration of CONIEL without instruction of the physician.
(2) The administration of CONIEL may cause excessive reduction in blood pressure and consequently transient unconsciousness, etc. Appropriate measures such as reduction of the dosage and suspension of administration should be taken in that event.
(3) Since the antihypertensive activity of CONIEL may induce dizziness, etc., patients should be cautioned to pay much attention in engaging in potentially hazardous activities such as working at a height and driving a car.

3. Drug Interactions
This drug is mainly metabolized by CYP3A4.

Precautions for coadministration (CONIEL 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>Digoxin</td>
<td>Excessive reduction in blood pressure may occur.</td>
<td>Antihypertensive activities are enhanced.</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digitalis intoxication may occur. The blood concentration of digoxin and the condition of the heart should be monitored. The dosage of digoxin should be adjusted or administration of CONIEL should be discontinued if any abnormality is observed.</td>
<td>It has been reported that the tubular secretion of digoxin was inhibited by calcium antagonists resulting in an increase of blood concentration of digoxin.</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Excessive reduction in blood pressure may occur.</td>
<td>It has been reported that cimetidine reduced gastric acidity resulting in an increase of the absorption of drugs in the stomach, while it inhibited the enzymes metabolizing calcium antagonists in liver microsomes.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>The antihypertensive activity of CONIEL may be attenuated.</td>
<td>It has been reported that rifampicin induced the release of drug metabolizing enzymes, resulting in the stimulation of the metabolism of calcium antagonists and thereby decreasing the blood concentration of them.</td>
</tr>
</tbody>
</table>

4. Adverse Reactions
Adverse reactions (including abnormalities in laboratory data) were reported in 219 (4.7%) of 4,679 patients treated with CONIEL before approval and during the post-marketing drug use surveillance until October 1997. Main adverse reactions were palpitation (24 cases, 0.5%), facial hot flushes (22 cases, 0.5%) and headache (20 cases, 0.4%). (at the end of reexamination)

(1) Clinically significant adverse reactions
Hepatic function disorder, jaundice (incidence unknown): Hepatic function disorder or jaundice may occur with increases of AST (GOT), ALT (GPT) or γ-GTP. Patients should be carefully observed, and, if any abnormal change is noted, treatment should be discontinued and appropriate measures should be taken.

(2) Other adverse reactions
Such adverse reactions as listed in the below table may occur. Patients should be carefully observed and, if any abnormality occurs, appropriate measures such as reduction of the dosage and suspension of administration should be taken. Administration of CONIEL should be stopped if any of the adverse reactions listed in bold-face type occurs.

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (GOT) &gt; 500 IU/L</td>
<td>0.4%</td>
</tr>
<tr>
<td>ALT (GPT) &gt; 500 IU/L</td>
<td>0.4%</td>
</tr>
<tr>
<td>γ-GTP &gt; 1,000 IU/L</td>
<td>0.1%</td>
</tr>
<tr>
<td>Total bilirubin &gt; 3.5 mg/dl</td>
<td>0.1%</td>
</tr>
<tr>
<td>BUN &gt; 100 mg/dl</td>
<td>0.1%</td>
</tr>
<tr>
<td>Creatinine &gt; 2.0 mg/dl</td>
<td>0.1%</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>5% &gt; 5.0 x 10^9/L</td>
</tr>
<tr>
<td>Increased BUN, increased creatinine</td>
<td>5% &gt; 40 mg/dl, 5% &gt; 1.7 mg/dl</td>
</tr>
<tr>
<td>Leucopenia, eosinopenia</td>
<td>5% &gt; 1%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5% &gt; 150 x 10^9/L</td>
</tr>
<tr>
<td>Palpitation, facial flushes, decreased blood pressure</td>
<td>5% &gt;</td>
</tr>
</tbody>
</table>
5. Use in the Elderly
Since it is generally recognized that excessive reduction in blood pressure is not desirable in the elderly, it is recommended to start treatment with a low dose (2mg/day) and carefully monitor the patient’s condition during treatment.

6. Use during Pregnancy, Delivery or Lactation
(1) CONIEL should not be administered to pregnant women or women who may possibly be pregnant. [Fetal toxicity and, especially by administration in the perinatal period, prolongation of gestation and delivery time was observed in animal studies with rats and rabbits.]

(2) Administration of CONIEL is not recommended in nursing mothers. If, however, administration of CONIEL is indispensable, breast-feeding should be discontinued. [Excretion of this drug in breast milk was indicated in animal studies with rats.]

7. Pediatric Use
The safety of CONIEL in low-birth-weight babies, newborns, sucklings, infants or children has not been established (no clinical experience).

8. Overdosage
Overdosage of CONIEL may cause excessive reduction in blood pressure. If reduction in blood pressure is remarkable, appropriate measures such as lifting lower extremities, fluid therapy and administration of vasopressors should be taken. Hemodialytical removal of the drug is not effective because of its high rate of protein binding.

9. Precautions concerning Use
(1) Precautions for the use of divided 4 mg and 8mg tablets
Early use is recommended after dividing tablets (Store divided tablets in a light-proof container and use preferably within 60 days after dividing.)

(2) Precautions regarding dispensing
For drugs that 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 corner of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

10. Other Precautions
White turbid change of dialysis drainage has been reported in the patients undergoing continual ambulatory peritoneal dialysis (CAPD). In that event, discrimination from peritonitis, etc. is required.

PHARMACOKINETICS

1. Absorption
Plasma concentrations of unchanged benidipine hydrochloride changed as shown in the below figure after single oral administration of 2, 4 or 8mg of benidipine hydrochloride on fasting in 6 healthy male adults:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>T1/2 (hr)</th>
<th>AUC0–∞ (ng • hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 mg</td>
<td>0.55 ± 0.41</td>
<td>1.1 ± 0.5</td>
<td>–</td>
<td>1.04 ± 1.26</td>
</tr>
<tr>
<td>4 mg</td>
<td>2.25 ± 0.84</td>
<td>0.8 ± 0.3</td>
<td>1.70 ± 0.70</td>
<td>3.94 ± 0.96</td>
</tr>
<tr>
<td>8 mg</td>
<td>3.89 ± 1.65</td>
<td>0.8 ± 0.3</td>
<td>0.97 ± 0.34</td>
<td>6.70 ± 2.73</td>
</tr>
</tbody>
</table>

2. Distribution
- Distribution in tissues (data from an experiment with rats)
After oral administration of 1mg/kg of 14C-labelled benidipine hydrochloride in rats, the highest level of radioactivity, except in the gastric contents, was found in the liver followed by kidney, adrenal glands, submandibular gland, lung, pituitary gland and then pancreas. Only a small amount of the substance was transferred to the brain, spinal cord and testicle.

- Transfer (data from experiments with rats)

<table>
<thead>
<tr>
<th>Transfer to fetuses</th>
<th>Transfer to breast milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>When 1mg/kg of 14C-labelled benidipine hydrochloride was orally administered in pregnant rats, transfer of the drug to fetuses was demonstrated with radioactivity of less than 1/3 of that in the plasma of mother rats detected in fetuses.</td>
<td>After oral administration of 1mg/kg of 14C-labelled benidipine hydrochloride in nursing rats, the change of the concentration of the substance in breast milk resembled that of plasma concentration.</td>
</tr>
</tbody>
</table>
Mechanism of action

Benidipine hydrochloride combines with the DHP binding site of the potential-dependent calcium channel in the cell membranes and thereby inhibits calcium influx into cells and causes coronary and peripheral vessels to dilate. It is speculated that this drug, which is highly transferable into the cell membranes, combines with the DHP binding site mainly through the membranes. Studies on its inhibition of isolated vessels constriction and affinity for the DHP binding site have demonstrated a high affinity for and very slow dissociation from the DHP binding site and long-acting effects as well of this drug without material correlation with blood concentrations.

Plasma protein binding rate

<table>
<thead>
<tr>
<th>in vitro</th>
<th>98.46 to 98.93%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(human serum)</td>
<td>(1 to 100,000ng/mL of $^3$H-labelled benidipine hydrochloride)</td>
</tr>
</tbody>
</table>

Mechanism of action

Benidipine hydrochloride combines with the DHP binding site of the potential-dependent calcium channel in the cell membranes and thereby inhibits calcium influx into cells and causes coronary and peripheral vessels to dilate. It is speculated that this drug, which is highly transferable into the cell membranes, combines with the DHP binding site mainly through the membranes. Studies on its inhibition of isolated vessels constriction and affinity for the DHP binding site have demonstrated a high affinity for and very slow dissociation from the DHP binding site and long-acting effects as well of this drug without material correlation with blood concentrations.

Excretion (data from a study in UK)

After single oral administration of 8mg of $^{14}$C-labelled benidipine hydrochloride in healthy male adults, the cumulative excretion rates of radioactivity were about 35% in urine and about 36% in feces in 48 hours. They were about 36% and about 59%, respectively in 120 hours.

Clinical studies

1. Hypertension

CONIEL was effective in 84.2% (443/526) of the patients with essential hypertension (moderate to mild). The usefulness of CONIEL was recognized in a double-blind study. The response rates were 94.4% (34/36) for severe hypertension and 82.4% (28/34) for renal parenchymal hypertension. (Response rates were estimated from the number of patients evaluated as "reduced blood pressure" or better.)

2. Angina pectoris

CONIEL was effective (improved or better) in 60.8% (110/181) of the patients with angina pectoris, namely in 59.2% (71/120) for effort angina and 63.9% (39/61) for effort/rest angina. The usefulness of CONIEL was recognized in a double-blind comparative study.

3. Metabolism

Metabolites detected in human plasma and urine as well as metabolism studies in laboratory animals suggest that benidipine hydrochloride is metabolized in humans mainly through elimination of a benzyl of the side chain at position 3 (N-dealkylation), hydrolysis of 1-benzyl-3-piperidyl ester at position 3 and methyl ester at position 5, oxidation of dihydropyridine ring and oxidation of methyl at position 2. This drug is mainly metabolized by CYP3A4.

4. Excretion (data from a study in UK)

After single oral administration of 8mg of $^{14}$C-labelled benidipine hydrochloride in healthy male adults, the cumulative excretion rates of radioactivity were about 35% in urine and about 36% in feces in 48 hours. They were about 36% and about 59%, respectively in 120 hours.

Pharmacology

1. Antihypertensive activity

When benidipine hydrochloride was orally administered in spontaneous hypertensive rats, DOCA-salt hypertensive rats or renal hypertensive dogs, long-acting antihypertensive activity with slow onset was demonstrated. Resistance to this drug has not been generated by long-time use. Once-daily administration of CONIEL in essential hypertensive patients provided steady antihypertensive effect for a period of 24 hours without affecting diurnal variation of blood pressure.

2. Antianginal activity

Benidipine hydrochloride significantly improved cardiac dysfunction and ischemic abnormality on ECG in experimental animal model (rat) and coronary artery occlusion and reperfusion model (dog). Oral administration of CONIEL in patients with effort angina improved the exercise-induced ischemic abnormality on ECG. In patients with effort angina, the exercise-induced ischemic abnormality (ST depression on ECG) was significantly improved by 10mg of CONIEL three times daily.

3. Renal function sustaining activity

Consecutive oral administration of benidipine hydrochloride in spontaneous hypertensive rats with renal insufficiency (5/6 nephrectomized) provided antihypertensive effect and improved renal function. This drug significantly increased the renal blood flow in essential hypertensive patients. Additionally, this drug significantly increased creatinine clearance and urea nitrogen clearance in chronic renal insufficiency patients complicated with hypertension, demonstrating a renal function sustaining activity.

Physicochemistry

Nonproprietary name:
Benidipine Hydrochloride

Chemical name:
3-[(3R)-1-Benzylpiperidin-3-yl]5-methyl(4RS)-2,6-dimethyl-4-(3-nitrophenyl)1,4-dihydropyridine-3,5-dicarboxylate monohydrochloride

Molecular formula:
C$_{34}$H$_{41}$N$_4$O$_{10}$·HCl = 542.02

Structural formula:

![Structural formula](image)

Description:
Benidipine hydrochloride occurs as a yellow crystalline powder.

Solubility:

It is very soluble in formic acid, soluble in methanol, sparingly soluble in ethanol (99.5) and practically insoluble in water.

**Melting point:**
Approx. 200°C (decomposition)

**Optical rotation:**
Methanol solution (1→100) shows no optical rotating power.

**Partition coefficient:**
logP\text{oct} = 3.79
[measured by flask-shaking method using n-octanol/pH7.4 buffer solution]

**PRECAUTIONS FOR HANDLING**
The use of a tablet cutter may not be appropriate for 4 mg and 8 mg tablets [The tablet may not be properly divided into two pieces.]

**PACKAGING**

**CONIEL Tablets 2:**
Boxes of 100 (10 tablets × 10), 500 (10 tablets × 50), 700 (14 tablets × 50) and 1,000 (10 tablets × 100) tablets in press-through packages
Bottles of 500 tablets

**CONIEL Tablets 4:**
Boxes of 100 (10 tablets × 10), 500 (10 tablets × 50), 700 (14 tablets × 50) and 1,000 (10 tablets × 100) tablets in press-through packages
Bottles of 500 and 1,000 tablets

**CONIEL Tablets 8:**
Boxes of 100 (10 tablets × 10) and 500 (10 tablets × 50) tablets in press-through packages
Boxes of 500 tablets

**REFERENCES**

4) Company data: Kobayashi, H. et al.: measurements of protein binding in human serum in vitro (No.1)
6) Company data: Uji, Y. et al.: Plasma concentration, urinary excretion and metabolites in urine after single oral administration in humans. (Phase I clinical studies)

**REQUEST FOR LITERATURE OR INQUIRY**
**ABOUT PRODUCT INFORMATION SHOULD BE MADE TO:**
Please request for the company data as well as literature cited in the REFERENCE to the following.

Medical Information Office
Kyowa Hakko Kirin Co., Ltd.
1-6-1, Otemachi, Chiyoda-ku, Tokyo
100-8185 Japan
0120-850-150 (toll free)
Tel: 03-3282-0069 Fax: 03-3282-0102
Open: 9:00-17:30 (except Saturday, Sunday, national holidays and company holidays)

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