CONTRAINDICATIONS (MUCODYNE® Tablets 250 and 500 mg are contraindicated in the following patients.)
Patients with a history of hypersensitivity to the drug

DESCRIPTION
Product description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>MUCODYNE® Tablets 250 mg</th>
<th>MUCODYNE® Tablets 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive ingredient</td>
<td>Croscarmellose sodium, polyvinyl alcohol (partially saponified), sucrose fatty acid ester, magnesium stearate, hypromellose</td>
<td>Croscarmellose sodium, polyvinyl alcohol (partially saponified), sucrose fatty acid ester, magnesium stearate, methylcellulose, hydroxypropylcellulose, talc</td>
</tr>
</tbody>
</table>

Dosage form | Film-coated tablets
Color | White
Size Diameter | 8.6 mm (KP-256), Long diameter: 15.1 mm, Short diameter: 6.6 mm (KP-777)
Thickness | 4.5 mm, 5.7 mm
Weight | About 280 mg, About 561 mg
Identification code | KP-256, KP-777

INDICATIONS
Expectoration for the following diseases:
Upper respiratory inflammation (pharyngitis, laryngitis), acute bronchitis, bronchial asthma, chronic bronchitis, bronchiectasis, and pulmonary tuberculosis.

DRAINAGE IN CHRONIC SINUSITIS

Drainage in chronic sinusitis

DOSAGE AND ADMINISTRATION
For oral use, the usual dose for adults is 500 mg of L-carbocisteine three times daily. The dose may be adjusted according to age and symptoms.

Dosage for each dosage form is shown below.

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Per dose</th>
<th>Dosing frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUCODYNE® Tablets 250 mg</td>
<td>2 tablets</td>
<td>Orally, three times daily</td>
</tr>
<tr>
<td>MUCODYNE® Tablets 500 mg</td>
<td>1 tablet</td>
<td></td>
</tr>
</tbody>
</table>

PRECAUTIONS
1. Careful Administration (These products should be administered with care in the following patients.)
   1) Patients with hepatic dysfunction
   [Hepatic dysfunction may be exacerbated.]
   2) Patients with heart failure
   [It has been reported that analogous drugs affected the symptoms with heart failure.]

2. Adverse Reactions
   <At date of approval on partial modification of Mucodyne® DS (Dry Syrup)>
Adverse reactions to these products were reported in 100 of 11,042 patients treated (0.91%). The most frequently observed adverse reactions were anorexia in 27 patients (0.24%), diarrhea in 19 patients (0.17%), abdominal pain in 15 patients (0.14%), and rash in 11 patients (0.10%). (Above incidence have been collected from the reports of Mucodyne® Tablets 250mg, Tablets 500 mg, Fine granules 50%, K10, Syrup 2%, Syrup 5% and DS (Dry Syrup)).
(1) Clinically significant adverse reactions
   1) Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome)
Oculomucocutaneous syndrome (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell syndrome) may occur. Patients should be carefully monitored. If any abnormal findings are observed, administration should be discontinued and appropriate measures must be taken.

2) Hepatic dysfunction, Jaundice
Hepatic dysfunction with increased AST(GOT), ALT(GPT), Al-P, LDH and/or jaundice may occur. Patients should be carefully monitored. If any symptoms are observed, administration should be discontinued and appropriate therapeutic measures must be taken.

3) Shock, anaphylactoid symptoms
Patients should be observed carefully because shock and anaphylactoid symptoms (such as dyspnoea, edema, urticaria, etc.) may occur. If any of abnormal findings are observed, administration should be discontinued and appropriate therapeutic measures must be taken.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th></th>
<th>5% &gt; ≥0.1%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-intestinal</td>
<td>Anorexia,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diarrhea,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>abdominal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>vomiting,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>abdominal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>distension,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>thirst etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Rash</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eczema,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Itching</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#: If any hypersensitive reactions are observed, administration of the drug should be discontinued.

3. Use in the Elderly
Since elderly patients often have reduced physiological function, careful supervision and measurement, such as reducing the dose are recommended.

4. Use during Pregnancy, Delivery or Lactation
Use of these products is not recommended in pregnant women or in women who may possibly be pregnant. [The safety of these drugs in pregnant women has not been established.]

5. Precautions Concerning Use
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, its sharp corners may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

PHARMACOKINETICS
1. Blood concentrations

Blood concentrations and pharmacokinetic parameters of L-carbocisteine after single oral dose of 500 mg to the healthy adults are shown below.\(^{1,2}\)

![Blood concentrations (Healthy adults)](image)

Pharmacokinetic equality of each dosage form was confirmed.

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Tmax (hr)</th>
<th>Cmax (µg/mL)</th>
<th>t1/2 (hr)</th>
<th>AU/C0→7 (µg•hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets 250mg</td>
<td>500</td>
<td>2.2</td>
<td>4.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Tablets 500mg</td>
<td>500</td>
<td>2.3</td>
<td>3.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

CLINICAL STUDIES
The clinical efficacy of these products in clinical studies including double blind comparative studies performed in 978 cases is summarized as follows.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excellent and good</td>
</tr>
<tr>
<td>Upper respiratory inflammation</td>
<td>62.4% (58/93)</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>71.9% (105/146)</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>51.6% (47/91)</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>40.1% (83/207)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>51.9% (40/77)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>29.5% (23/78)</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>46.9% (134/286)</td>
</tr>
</tbody>
</table>

Clinical usefulness of these products has been established in double blind comparative studies for bronchial asthma, chronic bronchitis, bronchiectasis, pulmonary tuberculosis and chronic sinusitis.

PHARMACOLOGY
1. Effect on respiratory tract

1) Normalizing effect on mucous components
L-Carbocisteine normalizes the ratio of sialic acid and fucose in sputum from patients with chronic airway diseases.\(^{3}\) L-Carbocisteine normalizes sulfur dioxide
exposure-induced changes in activity of sialic acid/fucose-splitting enzyme and sialic acid/fucose synthase. At the same time, L-Carbocisteine inhibits the increase of mucin (Muc-5ac protein) production, which is the primary component of mucus secreted in rats.\(^4\)

2) Inhibitory effect on hyperplasia of goblet cells
L-Carbocisteine inhibits goblet cell hyperplasia of airway mucosa on histologic examination of patients with chronic airway diseases.\(^5\) L-Carbocisteine inhibits hyperplasia of goblet cells in the airways of rats exposed to sulfur dioxide.\(^6\)

3) Inhibitory effect on airway inflammation
L-Carbocisteine inhibits sulfur dioxide exposure-induced inflammatory cell infiltration, superoxide and elastase activity in rat airways.\(^6\) L-Carbocisteine inhibits human neutrophil activation mediated by fMLP.\(^8\)

4) Repairing effect on mucosa
L-Carbocisteine helps ciliated cells in bronchiolar mucosal epithelium of patients with chronic bronchitis to be repaired.\(^9\)

2. Effect on sinus

1) Improving effect on mucociliary transport
L-Carbocisteine improves the reduced nasal mucociliary clearance in patients with chronic sinusitis.\(^10\)

2) Repairing effect on mucosa
L-Carbocisteine relieves the damages on sinusal mucosa induced by endotoxin or sulfur dioxide and promotes mucosal repairing in rabbits.\(^11,12\)

PHYSICOCHEMISTRY

Nonproprietary name: L-Carbocisteine [JAN]

Chemical name:
\((2R)-2\text{-Amino-3-carboxymethylsulfanylpropanoic acid}\)

Molecular formula: C\(_5\)H\(_9\)NO\(_4\)S

Molecular weight: 179.19

Structural formula:

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H\(_2\)O
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Melting point: Approx. 186°C (Decomposition)

Description:
White crystalline powder, odorless and slightly acidic in taste.
Very slightly soluble in water and practically insoluble in ethanol.\(^95\)
Soluble in dilute hydrochloric acid solution or sodium hydroxide solution.

Partition coefficient:
0.0 (1-octanol/water system, pH 2.3 - 8.0, 20°C)

PACKAGING

MUCODYNE\(^\circ\) Tablets 250mg:
Boxes of 100 tablets (10 tablets x 10), 500 tablets (10 tablets x 50), 1,000 tablets (10 tablets x 100), 2,100 tablets (21 tablets x 100), 3,000 tablets (10 tablets x 300) in press-through packages, and bottles of 500 tablets.

MUCODYNE\(^\circ\) Tablets 500mg:
Boxes of 100 tablets (10 tablets x 10), 630 tablets (21 tablets x 30), 1,000 tablets (10 tablets x 100) and 2,100 tablets (21 tablets x 100) in press-through packages, and bottles of 500 tablets.

REFERENCES

1) Kamijo S.: Bioequivalence study of L-Carbocisteine tablets 250mg (In-house data)
2) Imai J.: Bioequivalence study of L-Carbocisteine tablets 500mg (In-house data)
11) Maeyama T. et al.: OTO-RHINO-LARYNGOLOGY TOKYO, 29 (Suppl. 6), 447, 1986

REQUEST FOR LITERATURE SHOULD BE MADE TO:
A request for in-house data mentioned in the References can also be made to the following.
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)

Manufactured and marketed by:
Kyorin Pharmaceutical Co., Ltd.
6, Kanda surugadai 4-chome, Chiyoda-ku, Tokyo 101-8311, Japan