DAREN® Capsules 1 mg

DAREN® Capsules 2 mg

<Emedastine Difumarate>

**DESCRIPTION**

1. **Composition**
   
   **Capsules 1 mg:**
   
   Each capsule contains 1 mg of Emedastine Difumarate. Sodium lauryl sulfate is also present as an inactive ingredient.
   
   **Capsules 2 mg:**
   
   Each capsule contains 2 mg of Emedastine Difumarate. Sodium lauryl sulfate is also present as an inactive ingredient.

2. **Product description**
   
   **Capsules 1 mg:**
   
   capsule (white caps, white bodies).
   
   **Capsules 2 mg:**
   
   capsule (white caps, white bodies).

<table>
<thead>
<tr>
<th>Brand name</th>
<th>DAREN Capsules 1 mg</th>
<th>DAREN Capsules 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient/content (content per capsule)</td>
<td>1 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Sodium lauryl sulfate</td>
<td>Sodium lauryl sulfate</td>
</tr>
<tr>
<td>Dosage form</td>
<td>White capsules</td>
<td>White capsules</td>
</tr>
<tr>
<td>Appearance</td>
<td><img src="capsule1mg.png" alt="capsule" /></td>
<td>![capsule2mg.png]</td>
</tr>
<tr>
<td>Size</td>
<td>No.4</td>
<td>No.4</td>
</tr>
<tr>
<td>Identification code</td>
<td>NR1 ORGANON</td>
<td>NR2 ORGANON</td>
</tr>
<tr>
<td>Weight</td>
<td>195 mg</td>
<td>195 mg</td>
</tr>
</tbody>
</table>

**INDICATIONS**

Allergic rhinitis, urticaria, eczema or dermatitis, pruritus, prurigo.

**DOSAGE AND ADMINISTRATION**

The usual adult dosage for oral use is 2~4 mg of Emedastine Difumarate daily in two divided doses after breakfast and before sleep.

**PRECAUTIONS**

1. **Careful Administration** (DAREN® should be administered with care in the following patients.)
   
   Patients with hepatic disorder or a history of hepatic disorder [hepatic dysfunction may be induced.]

2. **Important Precautions**
   
   (1) Since DAREN® may induce drowsiness, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car. Moreover, it could be an obstacle in daily life. Patients should be cautioned before administration.
   
   (2) Severe sleepiness is more likely to occur in patients receiving 4 mg/day than 2 mg/day.
   
   (3) When patients being treated with long-term steroid therapy want to reduce the amount of steroid by replacement with DAREN®, dosage reduction should be done gradually under well controlled observation.
   
   (4) When used in patients who show seasonal symptoms, administration should be started just before the beginning of the season when symptoms will go into full swing and continued to the end of the season.
3. Drug Interactions
Precautions for coadministration (DAREN® 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>psychotropic drugs</td>
<td>The effects of the drugs when used in combination may be intensified.</td>
<td>The effects may be intensified by the inhibition in the central nervous system caused by this product.</td>
</tr>
<tr>
<td>sedatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hypnotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>antihistamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alcohol</td>
<td>The adverse effects in the central nervous system caused by the drug (mainly sleepiness) may be intensified.</td>
<td></td>
</tr>
</tbody>
</table>

4. Adverse Reactions
Adverse reactions to this drug were observed in 1,040 (7.34%) of the 14,168 patients evaluated in both the drug approval investigations, and the drug use investigations conducted after the product’s launch. The reactions were: sleepiness (6.30%), malaise and weakness (0.61%), thirst (0.23%), abdominal pain (0.14%), light-headed feeling (0.13%), headache, including dull headache (0.11%), twilight state (0.10%), etc. Abnormal laboratory data on this drug were increases in: ALT(GPT) (0.21%), AST(GOT) (0.16%), LDH (0.13%), gamma-GT (0.10%), etc¹–⁵. If the following adverse reactions are observed, appropriate measures, such as reducing the dose or discontinuing the administration, should be taken. The incidence of adverse reaction was higher in women than in men.

(At the time of application for re-examination)

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>10% &gt; 25%</th>
<th>5% &gt; 20.1%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psyconeurologic</td>
<td>Numbness of tongue, transient amnesia</td>
<td>Sleepiness</td>
<td>Malaise and weakness, headache, dull headache, twilight state, light-headed feeling</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Thirst, abdominal pain</td>
<td>Nausea and vomiting, anorexia, stomach discomfort, feeling heavy stomach, feeling of enlarged abdomen, diarrhea, constipation</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Heart pounding, increased blood pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Use in the Elderly
Careful supervision on the occurrence of adverse effect(s) is required, and measures such as reducing the initial dose to 1 mg per administration (elderly patients often have reduced physiological function) should be taken.

6. Use during Pregnancy, Delivery or Lactation
(1) The product should be used in pregnant women and women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment (The safety of this product in pregnant women has not been established).
(2) Use of this drug in lactating women is not recommended. If treatment with this drug is judged to be essential, breast feeding must be discontinued during treatment (Animal studies (rats) have shown that the drug is excreted in breast milk.).

7. Pediatric Use
The safety of this drug in premature infants, neonates, suckling infants and children has not been confirmed. There is not sufficient clinical data in pediatric patients.
8. Effects on Laboratory Tests
This product inhibits allergen intracutaneous reaction. This drug should not be used before performing an allergen intracutaneous reaction test because of its inhibitory activity against the reaction.

9. Precautions concerning Use
(1) Precaution(s) during oral administration
This product is a sustained-release preparation. Patients should not bite the capsules.

(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 corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis).

CLINICAL STUDIES
The results of clinical studies of this drug in 958 patients, including a double-blind comparative study, are shown below. The usefulness of this drug was also confirmed in a double-blind comparative study in patients with allergic rhinitis and urticaria.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Improvement rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>43.5 (111/255 patients)</td>
</tr>
<tr>
<td>Urticaria (mainly chronic)</td>
<td>69.6 (272/391 patients)</td>
</tr>
<tr>
<td>Eczema / dermatitis</td>
<td>71.0 (115/162 patients)</td>
</tr>
<tr>
<td>Pruritus cutaneous</td>
<td>72.5 (66/91 patients)</td>
</tr>
<tr>
<td>Prurigo</td>
<td>74.6 (44/59 patients)</td>
</tr>
</tbody>
</table>

PHARMACOLOGY

1. Anti-allergic effect
Emedastine Difumarate (p.o.) inhibited anaphylactic shock in guinea pigs and passive cutaneous anaphylaxis in guinea pigs and rats. Emedastine Difumarate (p.o.) inhibited experimental allergic rhinitis in rats.

2. Anti-histamine effect
Emedastine Difumarate inhibited histamine-induced contraction of isolated guinea pig ileum (in vitro). This drug also inhibited histamine-induced death and increased vascular permeability in guinea pigs (in vivo).

3. Inhibitory effect on release of chemical mediators induced by antigen-antibody reaction
Emedastine Difumarate inhibited histamine release from rat peritoneal mast cells and histamine and leukotriene C4 releases from human peripheral leukocytes and lung tissue due to the antigen-antibody reaction (in vitro) in a concentration-dependent manner. This drug also inhibited the histamine release induced by passive peritoneal anaphylaxis in guinea pigs (in vivo).

4. Inhibitory effect on the substance P-induced histamine release
Emedastine Difumarate inhibited the substance P-induced histamine release from rat peritoneal mast cells at low concentrations (in vitro). This inhibitory effect on histamine release was due to the inhibition of Ca2+-release from intracellular Ca storage sites and the inhibition of Ca2+ influx into cells.

5. Inhibitory effect on eosinophilic migration and infiltration
Emedastine Difumarate inhibited PAF-induced migration of guinea pig eosinophils in a concentration-dependent manner at concentrations of 10−8 M or more (in vitro). This drug also inhibited PAF- and leukotriene B4-induced migration of human eosinophils in a concentration-
dependent manner at concentrations of $10^{-8}$ M or more (in vitro$^{21}$).
In a nasal allergy guinea pig model, Emedastine Difumarate (p.o.) inhibited the infiltration of eosinophils to nasal mucosa$^{22}$.

**PHYSICOCHEMISTRY**

Nonproprietary name: Emedastine Difumarate (JAN)

Chemical name:

1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl) benzimidazole difumarate

Molecular formula: $C_{17}H_{26}N_{4}O \cdot 2C_{4}H_{4}O_{4}$

Molecular weight: 534.57

Structural formula: 

\[
\begin{array}{c}
\text{N} \\
\text{CH}_{2} \text{CH}_{2} \text{OCH}_{2} \text{CH}_{3}
\end{array} \quad \text{HOOCCH} \quad \text{・} \quad \text{HCCOOH}
\]

Description:

Emedastine Difumarate occurs as a white to pale yellow crystalline powder with no odor. It is freely soluble in water, soluble in methanol, sparingly soluble in dehydrated ethanol, slightly soluble in glacial acetic acid, and practically insoluble in dehydrated ether.

Melting point: 148.5–151.5°C

**PACKAGING**

DAREN CAPSULES 1 mg:

- Boxes of 100, 500, 1,000 and 3,000 in press-through packages (PTP 10 capsules 10, 50, 100 and 300)

DAREN CAPSULES 2 mg:

- Boxes of 100, 500, 1,000 and 3,000 in press-through packages (PTP 10 capsules 10, 50, 100 and 300)

**REFERENCES**


**REQUEST FOR LITERATURE SHOULD BE MADE TO:**

Medical Services

Fax: +81-6-6921-8236

Nippon Organon K.K

5-90, Tomobuchi-cho 1-chome, Miyakojima-ku, Osaka, Japan 534-0016

**Manufactured by:**

Nippon Organon K.K

5-90, Tomobuchi-cho 1-chome, Miyakojima-ku, Osaka, Japan 534-0016

**BRAND NAMES IN OTHER COUNTRIES**

REMICUT (Korea)

EMADINE (U.S.A etc.)