Kyowa Hakko Kirin Co., Ltd.

Revised: July 2010 (14th version, Additional dosage and administration)

Standard Commodity Classification No. of Japan 87449

- ANTIALLERGIC AGENT -

**ALLELOCK® Tablets 2.5**

**ALLELOCK® Tablets 5**

<Olopatadine hydrochloride tablets>

**Storage**

Store at room temperature.

<table>
<thead>
<tr>
<th>Approval No.</th>
<th>Tablets 2.5 mg</th>
<th>Tablets 5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of listing in the NHI reimbursement price</td>
<td>February 2001</td>
<td>February 2001</td>
</tr>
<tr>
<td>Date of initial marketing in Japan</td>
<td>March 2001</td>
<td>March 2001</td>
</tr>
<tr>
<td>Date of latest reexamination</td>
<td>December 2009</td>
<td>December 2009</td>
</tr>
<tr>
<td>Date of latest approval of dosage and administration</td>
<td>Children: July 2010</td>
<td></td>
</tr>
<tr>
<td>International birth date</td>
<td>December 1996</td>
<td></td>
</tr>
</tbody>
</table>

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

Patients with a history of hypersensitivity to any of the components of the product

**DESCRIPTION**

1. **Composition**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>ALLELOCK Tablets 2.5</th>
<th>ALLELOCK Tablets 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>2.5 mg of olopatadine hydrochloride in each tablet</td>
<td>5 mg of olopatadine hydrochloride in each tablet</td>
</tr>
</tbody>
</table>

2. **Product description**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>ALLELOCK Tablets 2.5</th>
<th>ALLELOCK Tablets 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter</td>
<td>6.1 mm</td>
<td>7.1 mm</td>
</tr>
<tr>
<td>Thickness</td>
<td>3.0 mm</td>
<td>3.0 mm</td>
</tr>
<tr>
<td>Weight</td>
<td>0.08 g</td>
<td>0.12 g</td>
</tr>
<tr>
<td>Face</td>
<td>Light yellow-red film-coated tablets</td>
<td>Light yellow-red film-coated tablets</td>
</tr>
<tr>
<td>Reverse</td>
<td>KH020 (Printed on the tablets and PTP)</td>
<td>KH021 (Printed on the tablets and PTP)</td>
</tr>
</tbody>
</table>

**INDICATIONS**

Adults: Allergic rhinitis, urticaria, itching resulting from skin diseases (eczema/dermatitis, prurigo, pruritus cutaneous, psoriasis vulgaris, multiform exudative erythema)

Children: Allergic rhinitis, urticaria, itching resulting from skin diseases (eczema/dermatitis, pruritus cutaneous)

**DOSAGE AND ADMINISTRATION**

Adults: Usually, for adults, administer 5 mg as olopatadine hydrochloride twice a day orally in the morning and at bedtime.

The dose may be increased or decreased according to age and symptoms.

Children: Usually, for children over 7 years of age, administer 5 mg as olopatadine hydrochloride twice a day orally in the morning and at bedtime.

**PRECAUTIONS**

1. **Careful Administration (ALLELOCK should be administered with care in the following patients.)**

   (1) Patients with impaired renal function [There is a possibility of persistently elevated blood concentrations. See “PHARMACOKINETICS”].

   (2) Elderly patients [See “Use in the Elderly” and “PHARMACOKINETICS”].

   (3) Patients with hepatic dysfunction [Hepatic dysfunction may be aggravated].
2. Important Precautions

(1) Since ALLELOCK may induce drowsiness, patients should be cautioned against engaging in potentially hazardous activities requiring alertness such as operating machinery or driving a car.

(2) In case ALLELOCK is administered in the patients who have been under chronic treatment with a steroid, dose reduction of the steroid should be made gradually under careful supervision.

(3) In case ALLELOCK is administered in the patients with seasonal diseases, it is recommended to initiate administration immediately before the typical season to be continued until the end of the season.

(4) If ALLELOCK does not exhibit effect, administration should not be continued aimlessly for a prolonged time.

3. Adverse Reactions

<Adults>
The collective data from clinical trials before approval, drug use-results survey and special survey for long term use include a total of 1,402 adverse reactions reported from 1,056 patients (11.0%) among 9,620 patients treated. The major adverse reactions were sleepiness 674 events (7.0%), ALT (GPT) increased 68 events (0.7%), malaise 53 events (0.6%), AST (GOT) increased 46 events (0.5%), thirst 36 events (0.4%), etc. (at the end of reexamination).

<Children>
The collective data from clinical trials in Japan include a total of 78 adverse reactions reported from 62 patients (14.9%) among 417 patients treated. The major adverse reactions were sleepiness 22 events (5.3%), ALT (GPT) increased 18 events (4.3%), AST (GOT) increased 8 events (1.9%), leukocytosis 7 events (1.7%), γ-GTP increased 3 events (0.7%), etc.

(1) Clinically significant adverse reactions

Hepatic function disorder, jaundice (incidence unknown): Hepatic function disorder with increases of AST(GOT), ALT(GPT), γ-GTP, LDH, Al-P and T-Bil increased and jaundice may occur. Patients should be carefully observed, and, in the event of abnormalities, treatment should be discontinued and appropriate measures should be taken.

(2) Other adverse reactions

Since the following adverse reactions may occur, patients should be observed carefully. In the event of abnormalities, appropriate measures such as dose reduction or temporary discontinuation of administration should be taken.

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Psychoneurologic</th>
<th>Sleepiness</th>
<th>Malaise, thirst, headache/dull headache, dizziness</th>
<th>Numbness, mental concentration decreased</th>
<th>Involuntary movement (face, extremities, etc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td></td>
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<tr>
<td>&lt;5%, &gt;0.1%</td>
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<tr>
<td>&lt;0.1%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Gastrointestinal</th>
<th></th>
<th>Constipation, stomatitis/angular stomatitis, tongue pain, hoarfurn, increased appetite</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Abdominal discomfort, abdominal pain, diarrhea, nausea</td>
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<tr>
<td>&lt;5%, &gt;0.1%</td>
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<td></td>
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<tr>
<td>&lt;0.1%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Hepatic</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Hepatic function abnormal (AST(GOT), ALT(GPT), γ-GTP, LDH, Al-P and T-Bil increased)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;5%, &gt;0.1%</td>
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<td></td>
</tr>
<tr>
<td>&lt;0.1%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>hematologic</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Leukocytosis, leucopenia, eosinophilia, lymphopenia</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;5%, &gt;0.1%</td>
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<tr>
<td>&lt;0.1%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Renal and urinary</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Occult blood in urine, BUN increased</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%, &gt;0.1%</td>
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<td></td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Cardiovascular</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Palpitation, blood pressure increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%, &gt;0.1%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Others</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td>Serum cholesterol increased</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;5%, &gt;0.1%</td>
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<td></td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Urine sugar positive, chest discomfort, taste abnormality, weight increase, hot flushes</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%, &gt;0.1%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>Menstrual disorder, arthralgia, myalgia</th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5%, &gt;0.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.1%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*In case of the occurrence of these symptoms, administration should be discontinued.

4. Use in the Elderly

Since elderly patients often have reduced physiological function and are more likely to develop adverse reactions, ALLELOCK should be administered cautiously by starting at a low dose while monitoring the patient’s condition.

5. Use during Pregnancy, Delivery or Lactation

(1) ALLELOCK should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [Safety of the administration during pregnancy has not been established.]

(2) Lactating women should not be given ALLELOCK. If treatment with this drug is judged to be essential, breast feeding must be discontinued during treatment. [Animal studies (rats) reported excretion of this drug in breast milk and weight increase inhibition of the neonates.]
6. Pediatric Use
The safety of ALLELOCK in low-birth-weight babies, newborns, sucklings or infants has not been established (insufficient clinical experience).

7. Effects on Laboratory Tests
Since the administration of ALLELOCK inhibits the intradermal reaction to allergens and thus interferes with the identification of potential allergens, ALLELOCK should not be administered prior to intradermal allergen tests.

8. Precautions concerning Use

(1) Precautions regarding dispensing
For drugs dispensed in 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.]

(2) Cautions in the use of scored tablets
Tablets after divided should be stored in a light-proof container.

9. Other Precautions
It was reported that myocardial infarction occurred during treatment with this drug, though the causal relationship is unknown.

PHARMACOKINETICS

1. Absorption

(1) Healthy adults

1) Single dose

The mean plasma concentration-time profile and pharmacokinetic parameters after a single dose of 5 mg or 10 mg of olopatadine hydrochloride to healthy male adults under fasting are as follows. (measured by RIA)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>T1/2 (h)</th>
<th>AUC0-∞ (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>107±64 22.01</td>
<td>1.00±0.32</td>
<td>8.75±4.63*</td>
<td>326±63*</td>
</tr>
<tr>
<td>10 mg</td>
<td>191±78 42.99</td>
<td>0.92±0.47</td>
<td>7.13±2.21**</td>
<td>638±136**</td>
</tr>
</tbody>
</table>

2) Repeated dose

When 10 mg of olopatadine hydrochloride was orally administered to 8 healthy male adults by repeated administration of 13 doses, i.e. twice daily for 6 days and once on day 7, the plasma concentration reached the steady state before day 4 of administration. The Cmax was 1.14 times that after a single oral dose. (measured by RIA)

(2) Patients with impaired renal function (not on dialysis)

When a single dose of 10 mg of olopatadine hydrochloride was orally administered after breakfast to patients with impaired renal function (2.3 to 34.4 mL/min creatinine clearance), the mean plasma concentration-time profile is as follows. The Cmax and AUC in patients with impaired renal function were 2.3 and 8 times of those in healthy adults, respectively. (measured by RIA)

(3) The elderly

When a single dose of 10 mg of olopatadine hydrochloride was orally administered to elderly patients (not less than 70 years), the mean plasma concentration-time profile is as follows. The mean plasma concentration was higher than that in healthy adults. The Cmax and AUC in the elderly were 1.3 and 1.8 times of those in healthy adults, respectively, while T1/2 was generally similar in both groups (10 – 11 hours). (measured by RIA)

(4) Children

The mean plasma concentration-time profile and pharmacokinetic parameters after a single dose of 5 mg of olopatadine hydrochloride to children with allergic diseases (10 - 16 years old, 40 - 57 kg) are as follows. (measured by LC / MS / MS)
Pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>AUC0-12 (ng.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg</td>
<td>81.57±9.91</td>
<td>1.33±0.52</td>
<td>228±20</td>
</tr>
</tbody>
</table>

mean ± S.D.

2. Distribution

· Distribution in tissues (data from an experiment with rats)5)

After oral administration of 1 mg/kg of 14C-olopatadine hydrochloride in rats, the highest level of radioactivity was found 30 minutes after the administration in most tissues. Radioactivity in the liver, kidney, and urinary bladder as well as in the gastrointestinal tracts was higher than that in plasma.

· Permeability and transfer (data from an experiment with rats)5,6)

| Blood-brain barrier permeability | After oral administration of 1 mg/kg of 14C-olopatadine hydrochloride in rats, the level of radioactivity was lowest in the brain among the tissue measured and the Cmax was about 1/25 of that in plasma. |
| Blood-placental barrier permeability | After oral administration of 1 mg/kg of 14C-olopatadine hydrochloride in pregnant rats, the level of radioactivity in plasma and tissues of fetuses was 0.07 to 0.38 times that in plasma of mother rats. |
| Transfer to milk | After oral administration of 1 mg/kg of 14C-olopatadine hydrochloride in lactating rats, the AUC∞ of radioactivity in milk was about 1.5 times that in plasma. |

· Protein binding rate (in vitro ultrafiltration method)7)

| Added concentration (ng/mL) | Rate of protein binding in human serum (%) | 0.1 | 10 | 1000 |
|                           |                                           | 54.7 | 55.2 | 54.7 |

3. Metabolism8,9)

Metabolites in plasma after a single oral dose of 80 mg of olopatadine hydrochloride to healthy adults composed of about 7% of N-oxidative metabolite and about 1% of N-monodemethyl metabolite (AUC ratio to the unchanged body) and urinary metabolites composed of about 3% and about 1% of them (cumulative urinary excretion rates until 48 hours), respectively. (measured by LC / MS / MS)

4. Urinary excretion1)

(1) Healthy adults5)

Urinary excretion rate of the unchanged drug until 48 hours after a single oral dose of 5 mg or 10 mg of olopatadine hydrochloride in healthy adults was 63.0 to 71.8% of the administered dose. Urinary excretion rate after repeated administration of 13 doses at a dose of 10 mg twice daily for 6 days and once day 7 was also similar to that after a single oral dose. (measured by LC / MS / MS)

(2) Children6)

Urinary excretion rate of the unchanged drug until 12 hours after a single oral dose of 5 mg of olopatadine hydrochloride in children (10 - 16 years old, 40 - 57 kg) was 61.8% of the administered dose. (measured by LC / MS / MS)

CLINICAL STUDIES

<Adults>

The results of clinical studies including double blind comparative studies performed before approval can be summarized as follows:

1. Allergic rhinitis9)-11)

Olopatadine hydrochloride was effective in 62.9% (117/186) of the patients in the study conducted at 42 institutions in Japan.

In the double blind comparative study, the final global improvement rate (“improved” and better categories) was 62.4% (53/85) by olopatadine hydrochloride and 56.6% (47/83) by oxatomide. Non-inferiority test (Δ=10%) demonstrated equivalence (p=0.018). The overall safety rate (“no problem in safety”) was 68.0% (70/103) by olopatadine hydrochloride and 61.4% (62/101) by oxatomide, with no significant difference between the two groups (p=0.301; U test, p=0.403; χ² test).

2. Urticaria12)-15)

Olopatadine hydrochloride was effective in 80.6% (225/279) of the patients in the study conducted at 39 institutions in Japan.

In the double blind comparative study, the final global improvement rate (“improved” and better categories) was 77.7% (87/112) by olopatadine hydrochloride and 66.9% (81/121) by ketotifen fumarate. The main U test demonstrated significant improvement by olopatadine hydrochloride compared with ketotifen fumarate (p=0.019; U test, p=0.093; χ² test). Overall safety rate (“no problem in safety”) was 77.2% (95/123) by olopatadine hydrochloride and significantly higher than 53.9% (69/128) by ketotifen fumarate (p=0.0001; U test, p=0.0001; χ² test).

3. Itching caused by skin diseases (eczema/dermatitis, prurigo, pruritus cutaneous, vulgar psoriasis, multi-form exdative erythema)16)

In the general clinical study conducted at 31 institutions in Japan, olopatadine hydrochloride was effective in 74.6% (91/122) of the patients for eczema/dermatitis, 50.8%
Olopatadine hydrochloride principally acts as a selective histamine H₁ receptor antagonist. This drug also inhibits the production and release of chemical mediators.
(leukotriene, thromboxane, PAF, etc.) and the release of the neurotransmitter tachykinin.

2. Pharmacological action

(1) Anti-histaminic effect
Receptor binding experiments indicated that olopatadine hydrochloride possesses a potent antagonistic activity (Ki value: 16 nmol/L) against histamine H1 receptors but shows little affinity for muscarine M1 receptors. Its effect proved to be selective. Moreover, olopatadine hydrochloride has been shown to inhibit the histamine-induced bronchoconstriction in guinea pigs.

(2) Anti-allergic effect in experimental models
In experimental models of allergic rhinitis (guinea pigs, rats), olopatadine hydrochloride inhibited the increase of vascular hyperpermeability and nasal obstruction induced by antigen challenge. Olopatadine hydrochloride potently inhibited passive cutaneous anaphylaxis and anaphylactic bronchoconstriction in rats and guinea pigs.

(3) Effects on production and release of chemical mediators
Olopatadine hydrochloride inhibited the release of histamine from rat peritoneal mast cells (IC50 value; 72 µmol/L: when stimulated with ovalbumin, 110 µmol/L: when stimulated with dimetaphenylated bovine serum albumin, 26 µmol/L: when stimulated with A-23187, 270 µmol/L: when stimulated with compound 48/80) and also acted on arachidonic acid metabolism to inhibit the production or release of lipid mediators such as leukotriene (IC50 value: 1.8 µmol/L), thromboxane (IC50 value: 0.77 µmol/L), PAF (production: 52.8% inhibition at 10 µmol/L, release: 26.7% inhibition at 10 µmol/L) from human neutrophils.

(4) Inhibitory effect on the release of tachykinin
The neurotransmitter tachykinin released from the sensory nerve terminal is known to be involved in the onset and aggravation of allergic diseases. Olopatadine hydrochloride inhibited the tachykinin mediated contraction caused by electrical field stimulation in the preparation of the main bronchial muscle from guinea pigs (IC50 value; 5.0 µmol/L). This effect is considered to be due to the inhibition of the release of tachykinin by potassium channel activation (SKCa channel: small conductance Ca2+-activated K+ channel).

PHYSICOCHEMISTRY
Nonproprietary name: Olopatadine Hydrochloride
Chemical name: (Z)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepine-2-acetic acid monohydrochloride
Molecular formula: C21H23NO3·HCl=373.87
Structural formula:

\[
\begin{align*}
\text{CH}_3 & \\
\text{N} & \\
\text{C}_2 & \\
\text{O} & \\
& \text{HCl}
\end{align*}
\]

Description:
Olopatadine hydrochloride occurs as a white crystal or crystalline powder. It is odorless and has a bitter taste.

Solubility:
It is very soluble in formic acid, sparingly soluble in water and very slightly soluble in ethanol (99.5).

Melting point: About 250°C (decomposition)
Partition coefficient:
log \( P'_{OCT} \) = 0.3 (measured by Flask-shaking method using n-octanol/pH 7.4 buffered solution)

PACKAGING
ALLELOCK Tablets 2.5:
Boxes of 100 tablets (10 tablets x 10), 500 tablets (10 tablets x 50), 700 tablets (14 tablets x 50) and 1,000 tablets (10 tablets x 100) in press-through packages
Bottles of 500 tablets

ALLELOCK Tablets 5:
Boxes of 100 tablets (10 tablets x 10), 500 tablets (10 tablets x 50), 700 tablets (14 tablets x 50), 1,000 tablets (10 tablets x 100) and 3,000 tablets (10 tablets x 300) in press-through packages
Bottles of 500 tablets

REFERENCES
4) Company data: Pharmacokinetic studies in children.
10) Company data: M. Okuda, et al.; Late Phase 2 clinical studies in patients with perennial allergic rhinitis.
Investigation of optimum dosage in double blind studies conducted at many institutions.


17) Company data: A. Yoneda; Summary of safety and efficacy in elderly patients (65 years or older) in clinical studies.

18) Company data: The double blind comparative studies for children with perennial allergic rhinitis.

19) Company data: A long-term administration study for children with allergic rhinitis.

20) Company data: The double blind comparative studies for children with atopic dermatitis.


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, Ohtemachi, Chiyoda-ku, Tokyo, Japan

100-8185 Japan
Tel: 03-3282-0069, 0120-850-150 (toll free)
Fax: 03-3282-0102
Open: 9:00-17:30 (except Saturday, Sunday and national holidays)

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