Leukotriene receptor antagonist
– Therapeutic drug for bronchial asthma and allergic rhinitis –

**ONON® Capsules 112.5mg**

< Pranlukast hydrate capsules >

### CONTRAINDICATIONS (ONON® Capsules is contraindicated in the following patients.)
Patients with a history of hypersensitivity to any of the ingredients of this product.

### DESCRIPTION

#### 1. Composition

<table>
<thead>
<tr>
<th>Brand name</th>
<th>ONON® Capsules 112.5mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient/content (Content per capsule)</td>
<td>Pranlukast hydrate 112.5 mg</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Macrogol 4000, magnesium stearate, lactose hydrate (Capsules containing gelatin, macrogol 4000, sodium lauryl sulfate and titanium oxide)</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Hard capsules</td>
</tr>
</tbody>
</table>

#### 2. Product description

<table>
<thead>
<tr>
<th>Appearance</th>
<th>No. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (mg)</td>
<td>About 229</td>
</tr>
<tr>
<td>Color Cap</td>
<td>White - yellowish white opaque</td>
</tr>
<tr>
<td>Color Body</td>
<td>White - yellowish white opaque</td>
</tr>
<tr>
<td>Identification code</td>
<td>ONO 678</td>
</tr>
</tbody>
</table>

### INDICATIONS

Bronchial asthma
Allergic rhinitis

### DOSAGE AND ADMINISTRATION

The usual adult dosage for oral use is 450 mg of pranlukast hydrate (4 capsules) daily in two divided doses after each meal in the morning and evening. The dosage may be adjusted according to the patient’s age and symptoms.

### PRECAUTIONS

#### 1. Important Precautions

1. The patient should be well informed beforehand that ONON® can not be expected to alleviate existing attacks, unlike bronchodilators, steroids, etc.
2. When any severe attack occurs in patients with bronchial asthma receiving this product, bronchodilators or steroids should be administered.
3. When this product is used to reduce the dose of steroids in patients undergoing long-term steroid therapy, the dose of steroids should be reduced gradually with adequate monitoring.
4. When administration of this product is discontinued in patients in whom the maintenance dose of steroids has been successfully reduced with the use of this product, attention should be paid because the primary disease may relapse.
5. It has been reported that vasculitis consistent with Churg-Strauss syndrome occurred during the use of leukotriene receptor antagonists including this product. These symptoms usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid. When this product is used, attention should be paid especially to the change of eosinophilic count and vasculitis symptoms such as numbness, weakness of limbs, pyrexia, arthralgia and pulmonary infiltration.
6. Since psychiatric symptoms including depression, suicidal thinking, suicide and aggressive behavior have been reported in patients receiving other leukotriene antagonists, though the causal-relationship is not clear, the patient’s condition should be closely observed when ONON® is administered.
7. When no efficacy of this product is observed, the therapy with this product should not be continued aimlessly for a long-term period.
2. Drug Interactions

Precautions for coadministration (ONON® should be administered with care when coadministered with the following drugs.)

<table>
<thead>
<tr>
<th>Drugs mainly Metabolized by CYP3A4</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>erythromycin, etc.</td>
<td>The blood concentration of this drug and these may be increased.</td>
<td>It has been reported in an in vitro study that this drug is metabolized by CYP3A4, and competitively inhibits the metabolism of these drugs.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs that inhibit CYP3A4 (itraconazole, erythromycin, etc.)</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>(itraconazole, erythromycin, etc.)</td>
<td>The blood concentration of this drug may be increased.</td>
<td>It has been reported in an in vitro and in vivo studies that the metabolism of this drug is inhibited by these drugs. (See the section of “Pharmacokinetics”)</td>
</tr>
</tbody>
</table>

3. Adverse Reactions

<Bronchial asthma>
Two hundred and sixteen adverse reactions to ONON®, including abnormal laboratory test values, were observed in 200 (4.7%) of 4,963 patients evaluated in the clinical studies conducted up to the time of approval and in the Drug Use Investigation. The major adverse reactions were rash, itching, etc. in 30 cases (0.6%), abdominal pain-stomach discomfort in 29 cases (0.6%), diarrhea in 19 cases (0.4%), nausea in 15 cases (0.3%), hepatic function abnormalities such as increases in AST(GOT)-ALT(GPT) in 17 cases (0.3%), increased bilirubin in 7 cases (0.1%) etc. (At the end of the reexamination period)

<Allergic rhinitis>
Two hundred and fifty eight adverse reactions to ONON®, including abnormal laboratory test values, were observed in 200 (4.7%) of 4,277 patients evaluated in the clinical studies conducted up to the time of approval and in the Drug Use Investigation. The major adverse reactions were rash, itching, etc. in 30 cases (0.6%), abdominal pain-stomach discomfort in 29 cases (0.6%), diarrhea in 19 cases (0.4%), nausea in 15 cases (0.3%), hepatic function abnormalities such as increases in AST(GOT)-ALT(GPT) in 8 cases (0.2%), increased bilirubin in 7 cases (0.1%) etc. (At the end of the reexamination period)

(1) Clinically significant adverse reactions

1) Shock or anaphylactoid symptoms

Shock or anaphylactoid symptoms (both incidences unknown) may occur. Patients should be carefully monitored. If any symptoms such as decreased blood pressure, consciousness disturbance, dyspnea and rash are observed, administration should be discontinued and appropriate measures be taken.

2) Leukopenia

Leukopenia (incidence unknown, early symptoms: pyrexia, pharyngalgia, malaise, etc.) may occur. If such symptoms are observed, administration should be discontinued.

3) Thrombocytopenia

Thrombocytopenia (incidence unknown, early symptoms: purpura, epistaxis, bleeding tendency such as gingival bleeding, etc.) may occur. If such symptoms are observed, administration should be discontinued.

4) Hepatic function disorder

Hepatic function disorder (incidence unknown) with jaundice, remarkable increased AST(GOT)-ALT (GPT), etc. may occur. Patients should be carefully monitored. In the event of such cases, administration should be discontinued and appropriate measures should be taken.

5) Interstitial pneumonia or eosinophilic pneumonia

Interstitial pneumonia (incidence unknown) or eosinophilic pneumonia (0.02%) with pyrexia, coughing, dyspnea, chest X-ray abnormalities, eosinophilia, etc. may occur. If such symptoms are observed, administration should be discontinued and appropriate therapeutic measures such as administering adrenocortical hormones be taken.

6) Rhabdomyolysis

Rhabdomyolysis (incidence unknown) may occur. If any symptoms such as myalgia, feelings of weakness, increased CK (CPK) and increased blood myoglobin are observed, administration should be discontinued and appropriate measures be taken. In addition, attention should be paid to the occurrence of acute renal failure due to rhabdomyolysis.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash, itching, etc.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Arthralgia (tachycardia, atrial fibrillation, extrasystole, etc.), palpitation, flushing</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, abdominal pain, stomach discomfort, diarrhea</td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Headache, sleepiness, dizziness</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Increased bilirubin, increased AST (GOT)-ALT (GPT), etc.</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgia</td>
</tr>
</tbody>
</table>

*Incidence unknown
<table>
<thead>
<tr>
<th>Urinary</th>
<th>Proteinuria, urinary occult blood, pollakiuria</th>
<th>Decreased urine volume, impaired urination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td>Chest tightness, pyrexia, edema, malaise, increased triglyceride, hemorrhage, eosinophilia, pharyngolaryngeal abnormal feeling, dry mouth, tinnitus</td>
<td>Alopecia, menstrual irregularity, breast swelling or induration, mastalgia, gynecomastia</td>
</tr>
</tbody>
</table>

*: The ADR classified into “Incidence unknown” is the one collected from spontaneous reports.

Note) If such symptoms are observed, appropriate therapeutic measures such as discontinuation of administration should be taken.

4. Use in the Elderly
Since the elderly often have reduced physiological function, careful supervision and measures such as reducing the dose (for example, one capsule each twice daily) are recommended.

5. Use during Pregnancy, Delivery or Lactation
This product 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 the treatment. [The safety of this product in pregnant women has not been established.]

6. Pediatric Use
The safety of this product in low birth weight infants, neonates, nursing infants, infants or children has not been established (Few clinical experience).

7. Precautions concerning Use
Precautions regarding dispensing:
For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the product 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.)

PHARMACOKINETICS

1. Blood concentration
When ONON® was administered orally to 5 healthy adults after meals at a single dose of 225 mg, the plasma concentration reached a maximum of 642.3 ± 151.0 ng/mL about 5 hours after administration and decreased with a half-life of about 1.2 hours.  

<table>
<thead>
<tr>
<th>Tmax  (hr)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-∞ (ng·hr/mL)</th>
<th>T1/2 (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2 ± 1.1</td>
<td>642.3 ± 151.0</td>
<td>2348.7 ± 471.3</td>
<td>1.15 ± 0.13</td>
</tr>
</tbody>
</table>

Data presented are means ± S.D.

2. Metabolism
Pranlukast hydrate was mainly metabolized by a hepatic drug-metabolizing enzyme cytochrome P450 (CYP3A4) (in vitro).  

3. Excretion
When ONON® was administered orally to 5 healthy adults after meals at a single dose of 225 mg, its urinary and fecal excretions were 0.24% and 98.9%, respectively, of the administered amount within 72 hours after administration. The main metabolite in the plasma, urine and feces was the hydroxide, and pranlukast hydrate was excreted in the urine mostly as the glucuronic acid conjugate.  

4. Protein binding
The protein binding rate to human serum was 99.7 - 99.8%. The main binding protein was albumin (in vitro, ultrafiltration method).  

5. (Reference) Drug interaction in animals (monkeys)
It has been reported that blood concentrations of pranlukast hydrate have been elevated (Cmax by 2.8-fold and AUC by 2-fold) in cynomolgus monkeys when coadministered with ketoconazole.

CLINICAL STUDIES

1. Bronchial asthma
(1) The usefulness of ONON® in the treatment of adult bronchial asthma was recognized in a double-blind comparative clinical study. The efficacy of this product was also ascertained in the alleviation of asthmatic symptoms, the reduction of the dose of concomitant drugs and the improvement of lung function.  
(2) ONON® was judged to have “markedly” or “moderately” improved in 217 (65.0%) of 334 patients in clinical studies including the double-blind comparative clinical study.
2. Allergic rhinitis

(1) The improvement rates of ONON® in the treatment of perennial allergic rhinitis by type of disease were 61.2% (79/129 patients) in the type including nasal obstruction and 54.5% (12/22 patients) in the one excluding nasal obstruction. Furthermore, the improvement rates by individual symptoms were 71.8% (94/131 patients) for nasal obstruction, 60.3% (76/126 patients) for nasal discharge and 54.4% (68/125 patients) for sneezing.6)

(2) ONON® was judged to have “markedly” or “moderately” improved in 235 (65.6%) of 358 patients in clinical studies including the double-blind comparative clinical study.7)

(3) No direct comparative clinical studies were performed between the ONON® mono-therapy group and the combination therapy group of ONON® and other anti-allergic drugs. Meanwhile, the comparative study conducted by the envelope method between the combination therapy group of ONON® and anti-allergic drugs and the anti-allergic drugs mono-therapy group showed to have “markedly” or “moderately” improved in 19 (73.1%) of 26 patients in the combination therapy group and in 6 (30.0%) of 20 patients in the mono-therapy group.8)

PHARMACOLOGY

1. Pharmacological effects

(1) Antagonistic effect against leukotriene (LT) receptor

In the pulmonary and nasal mucosal membrane fractions of guinea pigs, pranlukast hydrate selectively binds to the receptors of LTC₄, LTD₄ and LTE₄ and antagonizes their actions. It does not antagonize the actions of histamine, acetylcholine, serotonin, etc. and has almost no effect on arachidonic acid metabolizing enzymes (in vitro).9, 10)

(2) Inhibitory effect on airway constriction

1) When ONON® is administered orally to bronchial asthma patients, it inhibits the airway constrictive reaction induced by inhalation of LTC₄ or LTD₄.11)

2) When ONON® is administered orally to bronchial asthma patients, it inhibits immediate and late asthmatic responses induced by antigen inhalation.11)

3) ONON® inhibits the airway constrictive reaction in adult bronchospastic asthma patients.12)

4) When pranlukast hydrate is administered orally, it inhibits antigen-induced airway constriction of sensitized guinea pigs.13)

5) Pranlukast hydrate inhibits the LTC₄ or LTD₄ induced constriction of isolated airway smooth muscles of guinea pigs and humans (in vitro).8, 14)

(3) Inhibitory effect on airway hyperresponsiveness

1) When ONON® is administered orally to bronchial asthma patients, it inhibits the airway hyperresponsiveness to methacholine.15)

2) When pranlukast hydrate is administered orally to guinea pigs, it inhibits the airway hyperresponsive-ness to acetylcholine or histamine induced by antigen inhalation. When this drug is administered intravenously, it also inhibits the airway hyperresponsiveness to histamine induced by LTs.13, 16, 18)

4) Inhibitory effect on airway vascular hyperpermeability and mucosal edema (anti-inflammatory action)

1) When pranlukast hydrate is administered orally to guinea pigs, it inhibits antigen-induced airway vascular hyperpermeability.17)

2) When pranlukast hydrate is administered intravenously to guinea pigs, it inhibits the formation of airway mucosal edema induced by LTC₄ or LTD₄.18)

5) Lung function improving effect

When ONON® is administered orally to bronchial asthma patients, it improves one second forced expiratory volume (FEV₁.0) and peak expiratory flow (PEF).4, 19)

6) Inhibitory effect on increased nasal airway resistance

1) When ONON® is administered orally to the patients with perennial allergic rhinitis, it inhibits increased nasal airway resistance induced by antigen.20)

2) When pranlukast hydrate is administered orally to sensitized guinea pigs, it inhibits increased nasal airway resistance induced by antigen.21)

7) Inhibitory effect on nasal mucosal edema associated with eosinophil infiltration

When pranlukast hydrate is administered orally to sensitized guinea pigs, it inhibits antigen-induced nasal mucosal edema associated with eosinophil infiltration.21)

8) Inhibitory effect on nasal mucosal hypersensitivity

When pranlukast hydrate is administered orally to sensitized guinea pigs, it inhibits enhancement of sneezing reaction to histamine induced by antigen.22)

2. Mechanism of action

Pranlukast hydrate selectively binds to and blocks the action of leukotriene receptors, which are closely related to the basic pathogenesis of bronchial asthma. It consequently inhibits the constrictive reaction, vascular hyperpermeability, mucosal edema and hyperresponsiveness of the airway, and thereby improves clinical symptoms and the lung function in patients with bronchial asthma.

In addition, pranlukast hydrate selectively binds to and blocks the actions of leukotriene receptors, which suggestively play an important role in the onset of specific pathogenesis of allergic rhinitis characterized by three major symptoms of nasal obstruction, nasal discharge and sneezing. It consequently inhibits increased nasal airway resistance, nasal mucosal edema associated with eosinophil infiltration and nasal mucosal hypersensitivity, and thereby indirectly improves clinical symptoms such as sneezing, nasal discharge etc. induced by histamine, acetylcholine and other non-specific stimuli.
PHYSICOCHEMISTRY

Nonproprietary name:
Pranlukast Hydrate (JAN), Pranlukast (INN)

Chemical name:
4-Oxo-8-[4-(4-phenylbutoxy)benzoylamino]-2-(tetrazol-5-yl)-4H-1-benzopyran hemihydrate

Molecular formula: C\textsubscript{27}H\textsubscript{23}N\textsubscript{5}O\textsubscript{4}·\frac{1}{2}H\textsubscript{2}O

Molecular weight: 490.51

Structural formula:

![Structural formula of Pranlukast Hydrate](image)

Description:
Pranlukast hydrate occurs as a white to light yellow crystalline powder. It is odourless and tasteless. It is soluble in dimethylsulfoxide or N,N-dimethylformamide, very slightly soluble in ethanol (99.5), and practically insoluble in water, acetonitrile, dichloromethane or diethyl ether.

Melting point: 231 – 235°C (decomposed)

PACKAGING

ONON® Capsules 112.5 mg:
Boxes of 140, 420 and 1,400 capsules in press-through package and bottles of 100 and 700 capsules

REFERENCES

5) Pooled analyses of clinical data on <Bronchial asthma>. Internal data of Ono Pharmaceutical Co., Ltd.
7) Pooled analyses of clinical data on <Allergic rhinitis>. Internal data of Ono Pharmaceutical Co., Ltd.

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Copies of the company’s internal data cited in the list of references above can also be requested at the following address:

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Pharmacovigilance Division
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Tel: 0120-626-190

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