- LEUKOTRIENE RECEPTOR ANTAGONIST -
- ANTI-BRONCHIAL ASTHMA DRUG -
KIPRES® Fine Granules 4 mg

< The Japanese Pharmacopoeia Montelukast sodium granules >

CONTRAINDICATIONS (This product is contraindicated in the following patients.)
Patients who are hypersensitive to any component of KIPRES

DESCRIPTION
Product description

<table>
<thead>
<tr>
<th>Active ingredient in a pack of 0.5 g</th>
<th>Montelukast 4 mg: The Japanese Pharmacopoeia (JP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive ingredient</td>
<td>D-Mannitol, hydroxypropylcellulose, and magnesium stearate</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Fine granules</td>
</tr>
<tr>
<td>Color</td>
<td>White</td>
</tr>
<tr>
<td>Identification code</td>
<td>KP-373 (package)</td>
</tr>
</tbody>
</table>

INDICATIONS
Bronchial asthma

DOSAGE AND ADMINISTRATION
In principle, the dosage for pediatrics ≥1 year and <6 years of age is 4 mg as montelukast (one packet) orally administered once daily at bedtime.

PRECAUTIONS FOR DOSAGE AND ADMINISTRATION
(1) The dosage must not be individualized based on the bodyweight and/or age of the patient or the severity of symptoms. The drug should be taken thoroughly.
(2) After opening the packet, the drug should be taken immediately (within 15 minutes) since the drug is photosensitive. [See the "Precautions concerning Use" section.]

PRECAUTIONS

1. Important Precautions
   1) Pediatric patients and their guardians or appropriate substitutive persons should be informed that KIPRES should be taken continuously not only during periods of worsening asthma, but also while asthma is controlled.
   2) Because KIPRES differs from bronchial dilators, steroids, etc., it is not a drug to relieve existing asthma attacks. This fact must be fully explained to pediatric patients and their guardians or appropriate substitutive persons.
   3) If a major attack is observed when administering KIPRES to a bronchial asthma patient, a bronchial dilator or steroid must be administered.
   4) If the patient is receiving long-term steroid treatment and the plan is to reduce the amount of steroids by administering KIPRES, this should be accomplished gradually under strict supervision.
   5) If the patient has been able to reduce the amount of steroid support by administering KIPRES, be cautious about the possibility of reoccurrence of the original symptoms.
   6) Psychiatric symptoms including depression, suicidal ideation, suicide and aggressive behavior have been reported although a causal relationship with this drug is not clear. Therefore, the patient's condition should be sufficiently observed. (See the "Other Precautions" subsection)
   7) There are reports that Churg-Strauss syndrome-like angiitis have occurred during use of leukotriene antagonists, which includes KIPRES. These symptoms are mainly produced when reducing or suspending the use of oral steroids. When using KIPRES, be cautious about eosinophil count and angiitic symptoms (numbness, weakness of limbs, pyrexia, arthralgia, and infiltration of the lung, etc.)
   8) When the efficacy of KIPRES is not observed, therapy with KIPRES should not be continued randomly for a long-term period.
   9) In general, small children do not have ability of describing subjective symptoms. Therefore, in administration of this drug, the care taker should be given the instruction to take proper measures such as carefully observing the

Storage
Store at room temperature.

Expiration date
Indicated on the package.

Approval No. 21900AMY00034000
Date of listing in the NHI reimbursement price September 2007
Date of initial marketing in Japan October 2007
Date of latest reexamination March 2015
International birth date July 1997
condition of the patient and quickly notifying the physician in case of observing abnormalities.

2. Drug Interactions
This drug is mainly metabolized by the drug metabolizing enzymes cytochromes P450 (CYP) 2C8/2C9 and 3A4. [See the “PHARMACOKINETICS” section.]

[Careful coadministration (This drug should be coadministered with caution.]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Signs, symptoms and treatment</th>
<th>Mechanism and risk factors</th>
</tr>
</thead>
</table>
| Phenobarbital| The action of this drug may be reduced. | Phenobarbital induces CYP3A4, thereby promoting the metabolism of this drug. [See the “PHARMACOKINETICS” section.]

3. Adverse Reactions
Pediatrics ≥1 year and <6 years of age (Domestic Clinical Studies Results)
In clinical studies conducted in Japan, there have been 4 cases of adverse reactions observed in 3 (2.2%) out of 137 patients. The adverse reactions were headache in 1 case, nausea in 1 case, dry skin in 1 case, and rash in 1 case. The abnormality in laboratory test findings observed was Al-P increased in 2 cases. (At approval)
In the specific drug-use results survey conducted in Japan, 7 cases (including abnormal laboratory test values) of adverse reactions were observed in 6 patients out of 1,406 patients evaluated for safety (0.4%).

The adverse reactions were palpitations, gastroenteritis, proteinuria, dry throat, oropharyngeal discomfort, purpura, urticaria in 1 case each respectively (0.1%). (At the end of reexamination)

[Overseas Clinical Studies Results, Reference]
In long-term clinical studies conducted overseas in pediatric patients ≥6 months and <32 months of age with bronchial asthma 3), there have been 9 cases of adverse reactions observed in 8 (5.1%) out of 158 patients. The adverse reactions were hyperkinesia in 4 cases (2.5%), failure to thrive in 1 case (0.6%), change in bowel habit in 1 case (0.6%), vomiting in 1 case (0.6%), abnormal dreams in 1 case (0.6%), and sleep disorder in 1 case (0.6%). No abnormalities in laboratory test findings were observed. There was no clinically meaningful difference between the montelukast and the control (usual care) groups.

In long-term clinical studies conducted overseas in pediatric patients ≥2 years and <6 years of age with bronchial asthma 3), there have been 19 cases of adverse reactions observed in 12 (3.3%) out of 364 patients. The main adverse reactions were thirst in 3 cases (0.8%), headache in 3 cases (0.8%), abdominal pain in 2 cases (0.5%), and urticaria in 2 cases (0.5%). There have been 11 cases of abnormalities in laboratory test findings observed in 7 patients (2.0%). The main abnormalities were leukocyte count decreased in 3 cases and AST (GOT) increased in 2 cases. There was no clinically meaningful difference between the montelukast and the control (usual care) groups.

Pediatrics ≥6 years of age (Domestic Clinical Studies Results, Reference)
In clinical studies conducted in Japan, 2 cases of adverse reactions were reported in 2 (2.1%) out of 96 patients. The adverse reactions were urticaria-like rash, dizziness in 1 case (1.0%) each respectively. (At approval)
In the specific drug-use results survey conducted in Japan, 9 cases (including abnormal laboratory test values) of adverse reactions were observed in 8 patients out of 1,194 patients evaluated for safety (0.7%).

The adverse reactions were nausea in 2 cases (0.2%), vomiting, headache, tic, eczema, erythema multiforme, urticaria, flushing in 1 case each respectively (0.1%).

In the post-marketing clinical studies 4)5) conducted in Japan, 12 cases (including abnormal laboratory test values) of adverse reactions were observed in 9 patients out of 134 patients evaluated for safety (6.7%) .

The adverse reactions were protein urine present in 2 cases (1.5%), nausea, headache, menstrual disorder, affect lability, white blood cell count increased, protein total increased, blood bilirubin increased, blood creatine phosphokinase increased, blood urea increased, urobilinogen urine increased in 1 case each respectively (0.7%). (At end of reexamination)

[Overseas Clinical Studies Results, Reference]
In long-term clinical studies conducted overseas in pediatric patients with bronchial asthma 6), 13 adverse reactions were reported in 10 (5.8%) of 172 patients. The most frequently reported adverse reactions observed were headache (3 events, 1.7%), dyspepsia (2 events, 1.2%), and flatulence (2 events, 1.2%). Also, the abnormality in laboratory test findings observed was “increased total bilirubin” in 1 case.

Adults (Domestic Clinical Studies Results, Reference)
In clinical studies conducted in Japan, 66 adverse reactions were reported in 46 (8.8%) of 523 patients. The most frequently reported adverse reactions observed were diarrhea (9 events, 1.7%), abdominal pain (7 events, 1.3%), nausea (6 events, 1.1%), heart burn (5 events, 1.0%) and headache (5 events, 1.0%). Also, 80 abnormalities in laboratory test findings were observed in 49 patients of 507 patients and the most frequently reported abnormalities were increased ALT (GPT) (14 events in 505 patients), increased γ-GTP (9 events in 463 patients) and increased alkaline phosphatase (8 events in 476 patients).

1) Clinically significant adverse reactions
(1) Anaphylaxis (frequency unknown)
Since anaphylaxis may occur, close observation should be maintained. If symptoms appear, this drug should be discontinued immediately and appropriate measures should be taken.
(2) **Angioedema** (frequency unknown)
Since angioedema may occur, close observation should be maintained. If symptoms appear, this drug should be discontinued immediately and appropriate measures should be taken.

(3) **Fulminant hepatitis** (frequency unknown), **hepatitis** (frequency unknown), **hepatic dysfunction** (0.01%), **jaundice** (frequency unknown)
Since fulminant hepatitis, hepatitis, hepatic dysfunction and jaundice may occur, close observation should be maintained. If abnormalities are observed, this drug should be discontinued and appropriate measures should be taken.

(4) **Toxic epidermal necrolysis (TEN)** (frequency unknown), **oculomucocutaneous syndrome (Stevens-Johnson syndrome)** (frequency unknown), **erythema multiforme** (0.01%)
Since toxic epidermal necrolysis, oculomucocutaneous syndrome and erythema multiforme may occur, close observation should be maintained. If abnormalities are observed, this drug should be discontinued and appropriate measures should be taken.

(5) **Thrombocytopenia** (frequency unknown)
Thrombocytopenia (initial symptoms: bleeding tendency such as purpura, nose bleeding and gingival bleeding) may occur. Therefore, if such a symptom as this occurs, this drug should be discontinued and appropriate measures should be taken.

2) **Other adverse reactions**
If the following symptoms or abnormalities appear, appropriate measures such as discontinuation of therapy should be considered.

<table>
<thead>
<tr>
<th>Incidence unknown</th>
<th>&lt;0.1%</th>
<th>&lt;1%</th>
<th>0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric and nervous system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache, somnolence</td>
<td>Restlessness, insomnia, hallucination, dizziness, sensory abnormality (numbness)</td>
<td>Dream abnormalities, irritability, seizure, agitation, tremor, somnambulism, disorientation, mental concentration decreased, memory impairment, delirium</td>
<td></td>
</tr>
<tr>
<td>Rash pruritus, urticaria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary eosinophilia</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea, abdominal pain, epigastric discomfort, nausea</td>
<td>Heartburn, vomiting, constipation, stomatitis</td>
<td>Dyspepsia</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The adverse reaction frequency was calculated based on clinical studies, post-marketing surveys (drug-use-results survey, specific drug-use-results survey, and post marketing clinical studies) of Tablets, Chewable Tablets and Fine Granules conducted in Japan.

4. **Use during Pregnancy, Delivery or Lactation**
1) **KIPRES** should be administered to pregnant women or women suspected of being pregnant only when it is judged that the benefits from the treatment exceed the possible risks.

   [The safety of KIPRES in pregnant women has not been established. During worldwide marketing experience, congenital limb malformations have been reported in the offspring of women being treated with KIPRES during pregnancy. Most of these women were also taking other asthma medications during their pregnancy. A causal relationship between these events and KIPRES has not been established.]

   2) Caution should be used in the administration of KIPRES to nursing mothers.

   [In animal studies (rats), it has been reported that KIPRES is secreted into breast milk.]
The approved dosage of KIPRES is 4 mg as montelukast in pediatrics ≥1 year and <6 years of age.

5. Pediatric Use
1) For pediatrics ≥ 6 years old, montelukast chewable tablets 5-mg should be administered once daily at bedtime.
2) The safety of montelukast formulations in babies under 1 year of age, newborns and premature infants has not been fully established. [Due to lack of domestic experience with montelukast formulations]

6. Precautions concerning Use
1) KIPRES may be taken with or without food.
2) KIPRES can be taken either directly into the mouth or after mixing it with 1 teaspoonful of soft food (room temperature or below). Also, this drug can be taken after mixing it with 1 teaspoonful (approximately 5 mL) of baby formula or breast milk (room temperature or below). Drinks such as water can be taken after administration of this drug.
3) Since the drug is photosensitive, the packet should not be opened until ready to use. The drug should be immediately (within 15 minutes) taken when mixed with soft food, baby formula or breast milk, and the mixture should not be stored for future use.
4) Since the drug is photosensitive, the drug must not be repackaged.

7. Other Precautions
The result of a pooled analysis of 41 placebo-controlled clinical studies indicated that while suicidal ideation was observed in one out of 9,929 patients in the montelukast group, no suicidal ideation was observed in 7,780 patients in the placebo group.7) Also, the result of a separate pooled analysis of 46 placebo-controlled clinical studies indicated that behavior-related adverse experiences (including insomnia and irritability) were observed in 319 (2.73%) out of 11,673 patients in the montelukast group and 200 (2.27%) out of 8,827 patients in the placebo group. No statistically significant difference was observed between them.8)

PHARMACOKINETICS
1. Blood Concentrations
1) Children at One to Less Than Six Years of Age
(1) Domestic Clinical Studies Results
Following oral administration of montelukast fine granules 4-mg once daily for 4 weeks to pediatric patients ≥1 year and <6 years of age with mild-to-moderate bronchial asthma, individual plasma concentrations of montelukast at one point per patient (either at 1.0 - 2.1 hours or 12.0 – 20.9 hours after administration) were distributed around the mean plasma concentrations in healthy adults following oral administration of montelukast film-coated tablets 10-mg or in pediatric patients ≥9 years and <14 years with bronchial asthma following oral administration of montelukast chewable tablets 5-mg(Fig.1).9)

Fig. 1 Plasma concentrations of montelukast following oral administration of montelukast fine granules 4 mg once daily to pediatric patients ≥1 year and <6 years of age with bronchial asthma

○ Individual plasma concentrations of montelukast at one point per patient following oral administration of montelukast fine granules 4 mg once daily for 4 weeks to pediatric patients ≥1 year and <6 years of age with bronchial asthma, n=67
▲ The mean plasma concentrations in pediatric patients ≥9 years and <14 years of age with bronchial asthma following single oral administration of montelukast chewable tablets 5-mg [mean ± standard deviation], n=8
■ The mean plasma concentrations in 3 studies in healthy adults following single oral administration of montelukast film-coated tablets 10 mg [mean ± standard deviation], n=36 to 44

(2) Overseas Clinical Studies Results (Reference)
Following single oral administration of montelukast fine granules 4 mg to pediatric patients ≥6 months and <2 years of age with bronchial asthma in the fasted state, the maximum plasma concentration (C\text{max}) was reached in approximately 2 hours after administration. The geometric mean ratio of area under the plasma concentration-time curve (AUC) (95% confidence interval) of pediatric patients ≥6 months and <2 years of age with bronchial asthma and that of adults following administration of montelukast film-coated tablets 10-mg was 1.26 (1.02, 1.54), the geometric mean ratio of AUC of pediatric patients ≥6 months and <1 year of age with bronchial asthma and that of adults was 1.35 (0.97, 1.87), and the geometric mean ratio of AUC of pediatric patients 1 year of age with bronchial asthma and that of adults was 1.18 (0.97, 1.44) (Table 1).10)
Following single oral administration of montelukast film-coated tablets 10 mg to pediatric patients ≥2 years and <6 years of age with bronchial asthma in the fasted state, the \( \text{C}_{\text{max}} \) was reached in approximately 2 hours after administration. The geometric mean ratio of AUC (90% confidence interval) of pediatric patients with bronchial asthma to healthy adults (administered montelukast film-coated tablets 10 mg in the fasted state) was 1.05 (0.90, 1.22) (Table 2). 11

### For Healthy adults, data following single oral administration of montelukast film-coated tablets 10 mg are shown.

### 2. Pediatric Patients ≥ 6 months and <15 years old (n=15)

<table>
<thead>
<tr>
<th>Subject</th>
<th>( \text{AUC}_{\text{pop}} ) (ng•hr/mL)</th>
<th>( \text{C}_{\text{max}} ) (ng/mL)</th>
<th>( \text{T}_{\text{max}} ) (hr)</th>
<th>( t_{1/2} ) (hr)</th>
<th>Mean ratio of ( \text{AUC}_{\text{pop}} ) (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 Months and &lt; one year old (n=12)</td>
<td>3470.9 [499.3]</td>
<td>583.5 [84.8]</td>
<td>2.07 [0.28]</td>
<td>3.24 [0.36]</td>
<td>1.35 (0.97-1.87)</td>
</tr>
<tr>
<td>One year old (n=14)</td>
<td>3039.3 [212.5]</td>
<td>470.1 [40.7]</td>
<td>2.34 [0.14]</td>
<td>3.48 [0.20]</td>
<td>1.18 (0.97-1.44)</td>
</tr>
</tbody>
</table>

### 3. Effect of Meats\(^{12}\) [Overseas Clinical Studies Results (Reference)]

Following single oral administration of montelukast fine granules 4 mg with applesauce to healthy adults, the mean \( \text{T}_{\text{max}} \) was prolonged from 2.1 hours to 3.4 hours as compared to following single oral administration of montelukast fine granules 4 mg alone. The mean \( \text{C}_{\text{max}} \) following single oral administration of montelukast film-coated tablets 10 mg alone and with applesauce were 198.8 ng/mL and 182.8 ng/mL, respectively. The mean AUC\(_{0-\infty}\) following single oral administration of montelukast fine granules 4 mg alone and with applesauce were 1223.1 ng•hr/mL and 1225.7 ng•hr/mL, respectively.

### 4. Patients with Abnormal Hepatic Function\(^{13}\) [Overseas Clinical Studies Results (Reference)]

Following single oral administration of montelukast film-coated tablets 10 mg to hepatic cirrhosis patients with mild-to-moderate hepatic insufficiency, the mean AUC increased by 41% and mean \( t_{1/2} \) prolonged from 4.7 hours to 8.6 hours, as compared to those of adults.

### 2. Distribution

The binding of montelukast with human plasma proteins was 99.6%. Montelukast was more than 99% bound to both albumin and \( \alpha_1 \)-acid glycoproteins at physiological concentrations. 14

### 3. Metabolism

The main metabolites of montelukast in human are side chain methyl hydroxylated metabolites and benzylcyclic methylene hydroxylated metabolites. Cytochromes P450 (CYP) molecular species CYP2C8/2C9 and 3A4 are involved in the formation of these metabolites, and CYP2C8 is the main enzyme in the metabolism of montelukast. It has been confirmed that side chain methyl hydroxylated metabolites are further metabolized oxidatively to carboxylic acid metabolites. Based on further \( \text{in vitro} \) results, therapeutic plasma concentrations of montelukast do not inhibit CYP3A4, 2C9, 1A2, 2A6, 2C19, or 2D6. 15\(^{-18}\)

Also, other \( \text{in vitro} \) studies have shown that montelukast is an inhibitor of CYP2C8. However, data from an overseas clinical drug-drug interaction study (reference) involving montelukast and a representative drug primarily metabolized by CYP2C8 (rosiglitazone) demonstrated that montelukast does not inhibit CYP2C8 \( \text{in vitro} \). Therefore montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g. paclitaxel.)

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**Table 1 Pharmacokinetic parameters following single oral administration of montelukast fine granules 4 mg to pediatric patients 6 months and <2 years of age with bronchial asthma in the fasted state**

<table>
<thead>
<tr>
<th>Subject</th>
<th>( \text{AUC}_{\text{pop}} ) (ng•hr/mL)</th>
<th>( \text{C}_{\text{max}} ) (ng/mL)</th>
<th>( \text{T}_{\text{max}} ) (hr)</th>
<th>( t_{1/2} ) (hr)</th>
<th>Mean ratio of ( \text{AUC}_{\text{pop}} ) (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 Months and 1 year old (n=15)</td>
<td>2721 [164.4]</td>
<td>471.00 [65.27]</td>
<td>2.07 [0.30]</td>
<td>3.17 [0.20]</td>
<td>1.05 (0.90, 1.22)</td>
</tr>
<tr>
<td>Healthy adults (n=16)</td>
<td>2595 [164.5]</td>
<td>283.71 [54.35]</td>
<td>3.36 [0.60]</td>
<td>4.09 [0.09]</td>
<td>-</td>
</tr>
</tbody>
</table>

Value estimated by method of population pharmacokinetics [standard error]
(For healthy adults, data following single oral administration of montelukast film-coated tablets 10 mg are shown.)

**Table 2 Pharmacokinetic parameters following single oral administration of montelukast fine granules 4 mg to pediatric patients ≥2 years and <6 years of age with bronchial asthma in the fasted state**

<table>
<thead>
<tr>
<th>Subject</th>
<th>( \text{AUC}_{\text{pop}} ) (ng•hr/mL)</th>
<th>( \text{C}_{\text{max}} ) (ng/mL)</th>
<th>( \text{T}_{\text{max}} ) (hr)</th>
<th>( t_{1/2} ) (hr)</th>
<th>Mean ratio of ( \text{AUC}_{\text{pop}} ) (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Two and &lt; six years old (n=15)</td>
<td>2721 [164.4]</td>
<td>471.00 [65.27]</td>
<td>2.07 [0.30]</td>
<td>3.17 [0.20]</td>
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</tr>
</tbody>
</table>

Value estimated by method of population pharmacokinetics [standard error]
(For healthy adults, data following single oral administration of montelukast film-coated tablets 10 mg are shown.)
4. Excretion

1) Results of Domestic Clinical Studies (Reference)
Following single 400-mg oral administration of montelukast capsules to healthy adults, unchanged drug was not detected in the urine. 20)  
2) Results of Clinical Studies Conducted Overseas (Reference)
During the 5 days after single oral administration of 102 mg of radiolabeled montelukast capsules to healthy adults, 86% of the radioactivity was recovered in feces and 0.1% in urine. 21)

5. Coadministration with Other Agents (Results of Clinical Studies Conducted Overseas, Reference)

1) Phenobarbital22)
When 100 mg phenobarbital (repeated administration for 14 days) was administered to healthy adults and then montelukast film-coated tablets 10 mg (single administration) was orally coadministered, the AUC0-∞ of montelukast was reduced by approximately 40%.

2) Theophylline23)
When a high oral dose of montelukast capsules (200 mg qd repeated administration for 6 weeks or 200 mg tid repeated administration for 8 days) was coadministered with an oral dose of theophylline (250 mg single administration) to healthy adults or coadministered with an intravenous dose of theophylline (5 mg/kg single administration), a decrease in plasma concentrations of theophylline was observed. Theophylline plasma concentrations did not change when an oral 10-mg dose of montelukast film-coated tablets (repeated administration for 10 days) was coadministered with an intravenous dose of 5 mg/kg theophylline (single administration).

3) Prednisone and Prednisolone
Following oral coadministration of 200 mg montelukast capsules (repeated administration for 6 weeks) with 20 mg prednisone (single administration) to healthy adults, the AUC0-∞ of prednisone was significantly lowered compared with placebo group. However, the AUC0-∞ of prednisone was not changed between before and after the administration of 200 mg montelukast capsules within the same subjects. The pharmacokinetics of the active metabolite prednisolone was not changed. Co-administration of 200 mg montelukast capsules (repeated administration for 6 weeks) with 20 mg intravenous prednisolone (single administration) to healthy adults had no effect on the pharmacokinetics of either prednisone or prednisolone.

4) Oral Contraceptives24) (ethinyl estradiol/norethindrone 35 μg/1 mg)
Following oral coadministration of 100 mg montelukast capsules (repeated administration for 8 days) with oral contraceptives (ethinyl estradiol/norethindrone 35 μg/1 mg single administration) to healthy adults, the pharmacokinetics of either ethinyl estradiol or norethindrone was not affected.

5) Digoxin25)
Following oral coadministration of montelukast film-coated tablets 10 mg (repeated administration for 7 days) with 0.5 mg digoxin (single administration) to healthy adults, the pharmacokinetics of immunoreactive digoxin was not affected.

6) Warfarin26)
Following oral coadministration of montelukast film-coated tablets 10 mg (repeated administration for 7 days) with 30 mg warfarin (single administration) to healthy adults, the plasma total drug concentrations of warfarin were not affected. Also, no effect on prothrombin time of warfarin was observed. (Note) The approved dosage of KIPRES is 4 mg as montelukast in pediatrics ≥1 year and <6 years of age.

CLINICAL STUDIES

The results of domestic clinical studies9) in which montelukast fine granules 4 mg were administered once daily for 8 weeks to pediatric patients ≥1 years and <6 years of age with bronchial asthma are summarized in table 3.

Table 3 Efficacy of domestic clinical studies for pediatric patients ≥1 years and <6 years of age with bronchial asthma

<table>
<thead>
<tr>
<th>Item</th>
<th>Baseline (Found)</th>
<th>Week 4 (Changes)</th>
<th>Week 8 (Changes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of mild attacks</td>
<td>7.98 ± 9.26 (66)</td>
<td>-4.03 ± 8.18* (65)</td>
<td>-5.49 ± 8.09* (65)</td>
</tr>
<tr>
<td>Number of cough</td>
<td>19.98 ± 12.91 (66)</td>
<td>-6.81 ± 11.91* (65)</td>
<td>-8.54 ± 13.21* (65)</td>
</tr>
<tr>
<td>Score of treatment</td>
<td>58.28 ± 42.42 (66)</td>
<td>-4.17 ± 26.49 (65)</td>
<td>-11.80 ± 17.93* (65)</td>
</tr>
</tbody>
</table>

Mean ± standard deviation, ( ) : numbers of patients  
*p<0.001 (comparison to baseline, one-sample t-test)  
1: change from baseline  
A mild attack = an episode of mild wheezing occasionally associated with mild intercostal or tracheosternal retractions. Therapy score = treatment points counting status of concomitant drug use based on the Pediatric Asthma Treatment and Management Guideline 2000, Japan

PHARMACOLOGY

Mechanism of Action
Montelukast binds with high selectivity to type 1 cysteinyl leukotriene (CysLT1) receptors, thereby inhibiting the pathophysiologic actions (bronchoconstriction, vascular permeability, and mucus secretion) of the pro-inflammatory mediators LTD4 and LTE4. Due to this mechanism of action, montelukast significantly improves parameters of asthmatic inflammation contributing to its anti-asthmatic effect.

1. LT Receptor Antagonism (Receptor Binding Studies)
In receptor binding studies using membranes isolated from guinea pig lung, U937 and THP-1 cells, the binding of LTD4 to receptors was shown to be strongly inhibited by KIPRES and this inhibition was not affected by the presence of blood ingredients. On the other hand, a weak receptor antagonism against LTC4 and LTB4 was observed. 27)
2. Inhibitory Effect on Bronchoconstriction (Isolated Tissues and Animal Studies)
The LTD4-induced contractions were competitively inhibited by KIPRES in isolated guinea pig trachea. KIPRES was also shown to have a potent, continuous inhibitory action against LTD4-induced bronchoconstriction reactions in guinea pigs and squirrel monkeys. On the other hand, KIPRES did not block contraction of isolated tissues induced by LTC4 (in the absence of LTC4 metabolism). Also, there was almost no inhibition of bronchoconstriction in guinea pigs induced by histamine, arachidonic acid, serotonin and acetylcholine. 27)

3. Inhibitory Effect on Antigen-induced Bronchoconstriction
KIPRES inhibited antigen-induced bronchoconstriction reactions in sensitized inbred asthmatic rats, guinea pigs and squirrel monkeys when administered intravenously or orally. 27)
In overseas clinical studies, KIPRES inhibited early and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively. 28)

4. Inhibitory Effect on Immediate and Delayed Bronchoconstriction Reactions
KIPRES inhibited antigen-induced immediate and delayed bronchoconstriction reactions in sensitized squirrel monkeys when administered orally. 27)

5. Inhibitory Effect on Anaphylactic Shock
KIPRES partly inhibited anaphylactic shock induced by egg albumin in sensitized guinea pigs. 29)

6. Improvement of Pulmonary Function
KIPRES improved the forced expiratory volume in 1 second and peak expiratory flow in patients with mild-to-moderate chronic bronchial asthma. 30)

7. Effect on Eosinophils
KIPRES significantly reduced the sputum eosinophil to total leukocyte ratio in patients with mild-to-moderate chronic bronchial asthma, compared with placebo. 31)
Similarly, KIPRES significantly reduced the peripheral blood eosinophil to total leukocyte ratio in adults 30) and pediatric patients. 9), 32)

PHYSICOCHEMISTRY
Nonproprietary name: Montelukast Sodium (JAN)
Chemical name: Monosodium (1-2-[[1(R)-1-3-[[1(E)-2-7-chloroquinolin-2-yl]ethenyl]phenyl]-3-2-(1-hydroxy-1-methylethyl)phenyl]propyl)sulfanyl[methyl]cyclopropyl)acetate
Molecular formula: C_{35}H_{35}ClNNaO_{3}S
Molecular weight: 608.17
Structural formula:

\[
\text{Description: Montelukast Sodium occurs as a white to pale yellow-white powder. It is very soluble in methanol and in ethanol (99.5), and freely soluble in water. It is hygroscopic. It turns yellow on exposure to light. It shows a crystal polymorphism.}
\]

Partition coefficient: Log \(K_D=2.3\pm0.2\) in 1-octanol/phosphate buffered system (pH7)

PACKAGING
KIPRES Fine Granules 4 mg:
Aluminium-foil packet
28 packets (7 packets× 4)
100 packets (10 packets× 10)
140 packets (7 packets× 20)

REFERENCES
1) Analysis of adverse events in the domestic clinical studies in pediatric patients ≥1 year and <6 years of age with bronchial asthma (In-house data)
12) Food effects of montelukast fine granules 4mg (In-house data)
13) Pharmacokinetics of montelukast in patients with hepatic insufficiency (In-house data)
14) Binding of montelukast with proteins (In-house data)
17) Balani S.K., et al., Drug Metab. Dispos., 25(11), 1282 (1997)
29) Inhibitory effects of montelukast on anaphylactic shock (In-house data)

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