CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-829

FINAL PRINTED LABELING
SINGULAIR®
(MONTELUKAST SODIUM)
TABLETS AND CHEWABLE TABLETS

DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR®, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene (Cys-LT1) receptor.

Montelukast sodium is described chemically as (R)-[(E)-1, 11,13,15,17-eicosapentaenoyl]-1-[(1S)-(3R)-3-(2-chloro-3-quinuclidinyl) ethyl]-17-hydroxy-11-methylheptadecanoic acid, monosodium salt.

The empirical formula is C41H64ClNO9NaO2, and its molecular weight is 608.18. The structural formula is:

Montelukast sodium is hygroscopic, optically active, white to off-white powder. Montelukast sodium is hygroscopic in nature, methanol, and water and practically insoluble in acetone.

Each 10-mg film-coated SINGULAIR tablet contains 10.4 mg montelukast sodium, which is the molar equivalent to 10 mg of free acid, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methycellulose, hydroxypropyl cellulose, titanium dioxide, red iron oxide, yellow iron oxide, and cornstarch.

Each 5-mg chewable SINGULAIR tablet contains 5.2 mg montelukast sodium, which is the molar equivalent to 5.0 mg of free acid, and the following inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action

The cysteinyl leukotrienes (LTc4, LTD4, LTE4) are produced by arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These molecules bind to cysteinyl leukotriene receptors (Cys-LT1) found in the human airways. Cys-LT1 leukotrienes and leukotriene receptor activation have been correlated with the pathophysiology of asthma, including airway eosinophilia, smooth muscle contraction, and altered cellular activity associated with the inflammatory process, which contribute to the signs and symptoms of asthma.

Montelukast is an orally active compound that binds with high affinity and selectivity to the Cys-LT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or adrenergic receptors). Montelukast inhibits physiologic actions of LTD4 at the Cys-LT1 receptor without any agonistic activity.

Absorption

Montelukast is rapidly absorbed following oral administration. After a 10-mg film-coated tablet was given to fasting adults, the mean peak montelukast plasma concentration was achieved in 2 to 3 hours (Tmax). The mean oral bioavailability is 84%. The oral bioavailability and Cmax are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean Tmax is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning. The safety and efficacy of SINGULAIR were demonstrated in clinical trials in which both formulations were administered in the evening without regard to the timing of food ingestion.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal placental passage. Montelukast is not extensively metabolized in subjects after oral administration of montelukast 10 mg, and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (1.14x).

Special Populations

Gender: The pharmacokinetics of montelukast are similar in males and females.

Elderly: The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of compensated disease of decreased metabolism of montelukast resulting in increased plasma levels (50% Cmax, 85% higher mean montelukast AUC) under the plasma concentration area (AUC) following a single 10-mg dose. The elimination of montelukast was slightly prolonged compared with that in healthy subjects (mean T1/2 12.4 hours, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatic failure have not been evaluated.

Renal Insufficiency: Since montelukast and its metabolites are not eliminated in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Adolescent and Pediatric Patients: The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents 215 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients 215 years of age.

Pharmacokinetic studies show that the plasma profile of the 5-mg chewable tablet in pediatric patients 8 to 14 years of age is similar to that of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age.

Drug Interactions

Montelukast as a dose of 10 mg once daily caused no pharmacokinetic steady-state

- did not cause clinically significant changes in the kinetics of a single intravenous dose of theophylline (a primarily cytochrome P450 3A4 substrate).
- did not change the pharmacokinetic profile of warfarin, a substrate of cytochromes P450 2C9 and 2C19, or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the INR (international normalized ratio).
- did not alter the pharmacokinetic profile or urinary excretion of immunogenic digoxin.
- did not change the plasma concentration profile of terfenadine, a substrate of cytochrome P450 3A4, or fexofenadine, its benzylated metabolite, and did not prolong the QT interval following coadministration with terfenadine 60 mg twice daily.

Montelukast at doses of 100 mg daily resulted in no pharmacokinetic steady-state

- did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg and ethinyl estradiol 35 mcg.
- did not cause any clinically significant change in plasma profiles of prednisolone or prednisolone liposomes following administration of either oral prednisolone or intravenous prednisolone.

Phenobarbital, which induces hepatic metabolism, increased the AUC of montelukast approximately 40%, following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochromes P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.
SINGULAIR®
(MONTELUKAST SODIUM)
TABLETS and CHEWABLE TABLETS

Clinical Studies

There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing. Although the pharmacokinetics of montelukast are similar whether dosed in the morning or the evening, efficacy was demonstrated in clinical trials in adults and pediatric asthmatic patients. SINGULAIR® decreased morning peripheral blood eosinophils approximately 13 to 15% from baseline compared with placebo over the double-blind treatment period. The relationship between the observed and the clinical benefits noted in the clinical trials is not known only.

CLINICAL PHARMACOLOGY. Clinical Studies.

ADOLESCENTS AND ADULTS 15 YEARS OF AGE AND OLDER

Clinical trials in adolescents and adults 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily. This was shown in two chronic asthmatic trials using doses up to 200 mg once daily and in one exercise challenge study using doses up to 50 mg, evaluated at the end of the once-daily dosing interval.

This efficacy of SINGULAIR® for the chronic treatment of asthma in adolescents and adults 15 years of age and older was demonstrated in two U.S. and Multinational similar double-blind, randomized, 12-week, double-blind, placebo-controlled trials in 756 patients (785 treated with SINGULAIR® 5 mg, 785 treated with placebo, and 751 treated with active control). The patients treated with montelukast were mild and moderate, non-smoking asthmatics who required approximately 5 puffs of inhaler each day on an "as-needed" basis. The patients had a mean baseline percent of predicted forced expiratory volume in 1 second (FEV₁) 84% of predicted (approximately 70% of normal). The co-primary endpoints in these trials were FEV₁ and daytime asthma symptoms. Secondary endpoints included morning and evening peak expiratory flow rates (PMEF), peak flow variability, nocturnal awakenings due to asthma, and other asthma-related outcomes. In both studies after 12 weeks, a random subset of patients receiving SINGULAIR® was switched to placebo for an additional 3 weeks of double-blind treatment to evaluate for possible rebound effects. The results of the U.S. trial on the primary endpoint, FEV₁, expressed as mean percent change from baseline, are shown in Figure 1.

FIGURE 1

FEV₁, Mean Percent Change from Baseline (U.S. Trial)

![Graph showing FEV₁, Mean Percent Change from Baseline (U.S. Trial)]

The efficacy of SINGULAIR® on other primary and secondary endpoints is shown in Table 1 as compared analyses of the U.S. and Multinational trials.

TABLE 1

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>SINGULAIR®</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (Mean Change from Baseline) (U.S. Trial)</td>
<td>0.69</td>
<td>0.31</td>
</tr>
<tr>
<td>Peak Flow (Mean Change from Baseline) (U.S. Trial)</td>
<td>0.83</td>
<td>0.33</td>
</tr>
<tr>
<td>Daytime Symptoms (Mean Change from Baseline) (U.S. Trial)</td>
<td>0.83</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*The data are expressed as mean percent change from baseline.
In adult patients, SINGULAIR reduced "as-needed" p-amino-phenol use by 26.8% from baseline compared with 8.6% for placebo in patients with nocturnal awakenings of at least 5-minutes per week. SINGULAIR reduced the nocturnal awakenings by 31% from baseline, compared with 15.2% for placebo (t-test analysis).

SINGULAIR, compared with placebo, significantly improved other protocol-defined, asthma-related outcome measurements (see TABLE 2).

**TABLE 2**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>SINGULAIR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma Attack* 1% of patients</td>
<td>11.6%</td>
<td>18.4%</td>
</tr>
<tr>
<td>Oral Concomitant Use 1% of patients</td>
<td>16.7%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Daytime Symptom Score 10% of patients</td>
<td>1.6%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Asthma Exacerbations 1% of patients</td>
<td>12.6%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Asthma Control 1% of patients</td>
<td>38.5%</td>
<td>27.2%</td>
</tr>
<tr>
<td>Pharmacological Global Evaluation score†</td>
<td>1.77</td>
<td>2.62</td>
</tr>
<tr>
<td>Patients Global Evaluation score†</td>
<td>1.80</td>
<td>2.01</td>
</tr>
</tbody>
</table>

* Asthma Attack defined as utilization of healthcare resources such as an emergency room visit, a doctor's visit, emergency room follow-up, or hospitalization or an inpatient consultation.

** Asthma Exacerbation defined by symptoms that were in addition to those symptoms at baseline.

† Pharmacological/Global Evaluation score defined as the following: no change in asthma presentation, use of more than 7 of p-amino-phenol, or an asthma exacerbation.

In one of these trials, a non-U.S. formulation of inhaled beclomethasone dipropionate (treatment at 200 mcg twice daily with a spacer device was included as an active control. Over the 12-week treatment period, the mean percentage change in FEV1 over baseline for SINGULAIR and beclomethasone were 7.9% vs. 13.3% (p = 0.01) respectively; see FIGURE 2, and the change in day-time symptom scores were 0.69 vs. 0.57 on a 5 to 1 scale (p = 0.01) for SINGULAIR and beclomethasone, respectively. The percentages of individuals who achieved the SINGULAIR or beclomethasone, and the actual change in day-time symptom scores were 0.69 vs. 0.57 on a 5 to 1 scale showing a significant difference in FEV1 improvement between the two treatments.

**Oasis of Action and Maintenance of Benefits**

The efficacy of SINGULAIR in patients with asthma was measured by daily diary card parameters, including symptom scores, "as-needed" p-amino-phenol use, and FEV1, with all parameters being significantly higher in the SINGULAIR group compared to the placebo group. The results of these analyses were consistent with the overall findings of the study, indicating that SINGULAIR is effective in maintaining the improvement in asthma symptoms observed in the active control period.

**PIEDIGNE PATIENTS 6 TO 14 YEARS OF AGE**

The efficacy of SINGULAIR in patients 6 to 14 years of age was demonstrated in a 12-week double-blind, placebo-controlled, randomized trial. Patients treated with SINGULAIR and placebo using an inhaled p-amino-phenol had a mean baseline percent predicted FEV1 of 72% (approximately range, 40 to 90%) and a mean daily inhaled p-amino-phenol requirement of 3 to 4 puffs of metered-dose inhaler. Approximately 25% of the patients were on inhaled corticosteroids.

**FIGURE 2**

**FEV1**

Mean Percent Change From Baseline (Multinational Trial)

**FIGURE 3**

Distribution of Individual Patient Response (Multinational Trial)
in adult asthmatic patients with documented aspirin sensi-
tivity, by patients who were receiving concurrent inhaled
and/or oral corticosteroids, a 4-week randomized, placebo-
controlled, double-blind, parallel group study of SINGULAIR,
compared with placebo, resulted in significant improvement in pa-
timeters of asthma control. The magnitude of effect of SINGULAIR
in asthmatics sensitive to aspirin was similar to the effect observed
in the general population of asthmatic patients studied. The
subject of SINGULAIR in asthmatics sensitive to aspirin or other non-
esteroidal anti-inflammatory drugs in aspir-
in-sensitive asthmatic patients has been well evaluated in tese
PRECAUTIONS. General

EFFECTS ON EXERCISE-INDUCED BRONCH
CONSTRUCTION (ADULTS AND PEDIATRIC PATIENTS)

In a 12-week, randomized, double-blind, parallel group
study of 110 adolescent and adult asthmatics 15 years of age
and older, with a mean baseline FEV₁ percent predicted of
85% and with documented exercise-induced exacerbation of
asthma, treatment with SINGULAIR, 10 mg, once daily in the
evening, resulted in a statistically significant reduction in
mean maximal percent fall in FEV₁ and mean time to recovery
to within 5% of the pre-exercise FEV₁. Exercise challenge was
conducted at the end of the dosing interval (i.e., 20 to 24 hours
after the preceding dose). The effect was maintained through-
during the 12-week treatment period indicating that tolerance did
not occur. SINGULAIR did not, however, prevent clinically sig-
nificant asthma attacks in macronasal polycystic FEV₁ or
exercise (i.e., 130% decrease from pre-exercise baseline) in 52%
of patients studied. In a separate crossover study in adults,
a similar effect was observed after two once-daily 10-mg doses of
SINGULAIR.

In pediatric patients 6 to 14 years of age, using the 5-mg
chewable tablet, a 2-day crossover study demonstrated an
effects similar to those observed in adults when exercise chal-
lange was conducted at the end of the dosing interval (i.e.,
20 to 24 hours after the preceding dose). SINGULAIR
should not be used as monotherapy for the tretament and man-
agement of exercise-induced bronco-
spasm. Patients who have exacerbations of asthma after exer-
cise should continue to use their usual regimen of inhaled
beta-agonists as prophylaxis and have available for rescue
short-acting inhalant beta agonists (see PRECAUTIONS, General
and information for Patients).

INDICATIONS AND USAGE

SINGULAIR is indicated for the prophylaxis and chronic
management of asthma in adults and pediatric patients 6 years
and older.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

General

SINGULAIR is not indicated for use in the reversal of bron-
chospasm in acute asthma attacks, including status asthmaticus.

Patients should be advised to have proper rescue med-
cation available. They may be able to continue using SINGULAIR
can be continued during acute asthma exacerbations.

While the dose of inhaled corticosteroids may be reduced
great care should be undertaken when switching from SINGULAIR
should be gradually substituted for inhaled or oral corticosteroids.

SINGULAIR should not be used as monotherapy for the tretament and man-
agement of exercise-induced broncho-
spasm. Patients who have exacerbations of asthma after exer-
cise should continue to use their usual regimen of inhaled
beta-agonists as prophylaxis and have available for rescue
short-acting inhalant beta agonists (see PRECAUTIONS, General
and information for Patients).

Patients with known aspirin sensitivity should continue
avoidance of aspirin and non-steroidal anti-inflammatory ag-
ents while taking SINGULAIR. SINGULAIR is likely to be
effective in patients with aspirin sensitivity (see PRECAUTIONS,
General and information for Patients). Patients with aspirin
sensitivity and documented aspirin sensitivity, in adults with
exercise-induced asthma, and in adults with exercise-
induced asthma, have been observed to have rescue
short-acting inhalant beta agonists available as needed.

Patients with known aspirin sensitivity should continue
avoidance of aspirin and non-steroidal anti-inflammatory ag-
ents while taking SINGULAIR. SINGULAIR is likely to be
effective in patients with aspirin sensitivity (see PRECAUTIONS,
General and information for Patients). Patients with aspirin
sensitivity and documented aspirin sensitivity, in adults with
exercise-induced asthma, and in adults with exercise-
induced asthma, have been observed to have rescue
short-acting inhalant beta agonists available as needed.
SINGULAR®
(Metiamidex Sodium)
Tablets and Chewable Tablets

Generic Use
Of the total number of subjects in clinical studies of monotherapy, 3.5% were 65 years of age and over and 0.4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adolescents and Adults 15 Years of Age and Older
SINGULAR has been evaluated for safety in approximately 2600 adolescent and adult patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with SINGULAR occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo, regardless of causality assessment:

<table>
<thead>
<tr>
<th>Adverse Experience</th>
<th>SINGULAR 15 mg/day (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/tiredness</td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Fever</td>
<td>1.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Pain, abdominal</td>
<td>2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Trachea</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Rash</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Nervous System/Psychiatric Disorders</td>
<td>1.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Headache</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Respiratory System Disorders</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Cough</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Influenza</td>
<td>4.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Other AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>AST increased</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Pyuria</td>
<td>1.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

"Number of patients treated (SINGULAR and placebo, respectively): ALT and AST, 1,725, 1,110; pruritis, 1,238, 1,153.

The frequency of less common adverse events was comparable between SINGULAR and placebo.

Cumulatively, 169 patients were treated with SINGULAR for at least 6 months, 440 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

Pediatric Patients 6 to 14 Years of Age
SINGULAR has also been evaluated for safety in approximately 320 pediatric patients 6 to 14 years of age. Cumulatively, 169 pediatric patients were treated with SINGULAR for at least 6 months, and 121 for one year or longer in clinical trials. The safety profile of SINGULAR versus placebo in the double-blind, 6-week, pediatric efficacy trial was generally similar to the adult safety profile with the exception of the adverse events listed below. In pediatric patients receiving SINGULAR, the following events occurred at a frequency ≥1%: headache, respiratory symptoms, gastrointestinal, and viral infection. The frequency of less common adverse events was comparable between SINGULAR and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

OVERDOSAGE

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (approximately 2000 times the maximum recommended daily oral dose in adults and 2400 times the maximum recommended daily oral dose in children, on a mg/m² basis) and rats (approximately 4100 times the maximum recommended daily oral dose in adults and 4000 times the maximum recommended daily oral dose in children, on a mg/m² basis).

No specific information is available on the treatment of overdose with SINGULAR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 25 weeks and, in short-term studies, up to 900 mg/day to patients for approximately 6 weeks without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.
SINGULAIR:
Montelukast Sodium.
Tablets and Chewable Tablets

DOSAGE AND ADMINISTRATION

General Information:
Adolescents and Adults 15 Years of Age and Older
The dosage for adolescents and adults 15 years of age and older is one 10-mg tablet daily to be taken in the evening.

Pediatric Patients 6 to 14 Years of Age
The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet daily to be taken in the evening. No dosage adjustment within this age group is necessary. Safety and effectiveness in pediatric patients younger than 6 years of age have not been established.

The safety and efficacy of SINGULAIR was demonstrated in clinical trials where it was administered in the evening without regard to the time of food ingestion. There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing.

HOW SUPPLIED

No. 3760 — SINGULAIR Tablets, 5 mg, are pink, round, bi-convex-shaped chewable tablets, with code MRK 275 on one side and SINGULAIR on the other. They are supplied as follows:
NDC 0006-0275-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and a silica gel desiccant canister
NDC 0006-0275-54 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and a silica gel desiccant canister

NDC 0006-0275-26 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100.

No. 3761 — SINGULAIR Tablets, 10 mg, are beige, rounded square-shaped, film-coated tablets, with code MRK 117 on one side and SINGULAIR on the other. They are supplied as follows:
NDC 0006-0117-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, and aluminum foil induction seal, and a silica gel desiccant canister
NDC 0006-0117-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, and aluminum foil induction seal, and a silica gel desiccant canister

NDC 0006-0117-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100.

Storage
Store the 5-mg chewable tablets and the 10-mg film-coated tablets at room temperature 15-30°C (59-86°F), protected from moisture and light.

MERCK & CO., INC., West Point, PA 19486, USA

Issued February 1998
Printed in USA
IV. **LABELLING COMMENT**: (Needs to be sent to the sponsor)

The FDA version of PK subsection to be incorporated in the package insert is shown below:

*Pharmacokinetics*: Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

*Absorption*

For the 10-mg film-coated tablet, the mean peak plasma concentration ($C_{\text{max}}$) is achieved 3 to 4 hours ($T_{\text{max}}$) after administration to adults under the fasted state in the morning. The mean oral bioavailability is 64%. The oral bioavailability and $C_{\text{max}}$ are not influenced by a standard meal in the morning.

In one study, significant changes in $C_{\text{max}}$ (16%↓), $T_{\text{max}}$ (43%↑), and half-life ($T_{\text{1/2}}$; 26%↓) were found when the 10 mg film-coated montelukast tablet was given to healthy adults in the evening as compared to that in the morning under fasting conditions. In another study when the evening snack was given with the 10 mg film-coated tablet to healthy adults, minor changes in drug absorption were found except that the mean $T_{\text{max}}$ was significantly decreased from 4.2 hr to 2.6 hr as compared to the morning dose under fasting conditions.

For the 5-mg chewable tablet, the mean $C_{\text{max}}$ is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73%. The oral bioavailability (14%↓) and $C_{\text{max}}$ (48%↓) are significantly decreased and $T_{\text{max}}$ (74%↑) is significantly increased by a standard meal.
in the evening nor with evening snack in healthy adults or children.

Distribution
Montelukast is more than bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters.

Metabolism
Montelukast is extensively metabolized. In vivo metabolism study in humans show that parent compound, montelukast, predominated in plasma (>80-90% of total radioactivity). In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are nearly undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4 and 2C9 are involved in the metabolism of montelukast. Based on further in vitro results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma \( T_{1/2} \) of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg.

During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

Special Populations
Gender: The pharmacokinetics of montelukast are similar in males and females.
Elderly: The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma \( T_{1/2} \) of montelukast is longer (6.6 hours) and the plasma clearance is reduced (31 mL/min) in the elderly. No dosage adjustment in the elderly is required.
Race: Specific pharmacokinetic study for differences in races has not been conducted.

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in approximately 41% higher mean montelukast area under the plasma concentration curve (AUC) following a single 10-mg dose. The elimination of montelukast is slightly prolonged (mean \( T_{1/2} \), 7.4 hours) and plasma clearance is reduced (27 mL/min) as compared with those in healthy subjects. No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score > 9).
Renal Insufficiency: Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.
Adolescents and Pediatric Patients: The plasma concentration profile of montelukast following the 10-mg film-coated tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years of age.
Pharmacokinetic studies using either the chewable tablet or film-coated tablet show that the plasma profile of the 5-mg chewable tablet in pediatric patients 6 to 14 years of age is similar to that of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age.

**Drug Interactions**

Montelukast 10 mg once daily to pharmacokinetic steady state:

- did not cause clinically significant changes in the kinetics of an intravenous dose of theophylline.
- did not change the pharmacokinetic profile of warfarin or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the INR (International Normalized Ratio).
- did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin.
- did not change the plasma concentration profile of terfenadine or its carboxylated metabolite and did not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily.

Montelukast at doses of ≥ 100 mg daily to pharmacokinetic steady state:

- did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg /ethinyl estradiol 35 µg.
- did not cause any clinically significant change in plasma profiles of either prednisone and prednisolone following administration of either oral prednisone or intravenous prednisolone.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast; no dosage adjustment for montelukast is recommended (see PRECAUTIONS).

**Under the DOSAGE AND ADMINISTRATION section:** The words “and adolescents” should be added to the following text:

*Adults “and adolescents” 15 Years of Age and Older*

The dosage for adults “and adolescents” 15 years of age and older is one 10-mg tablet daily to be taken at bedtime.