CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20830/S1

APPROVAL LETTER

FEB 12 1999

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NDA 20-829/S-001
[redacted]

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point, PA 19486

Attention: William G. Roberts, M.D.
Director
Regulatory Affairs

Dear Dr. Roberts:

Please refer to your supplemental new drug applications dated March 19, 1998, received March 20, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singulair (montelukast sodium) Tablets, 10 mg (NDA 20-829), and Singulair (montelukast sodium) Chewable Tablets, 5 mg (NDA 20-830).

We also refer to your submissions dated August 20, 1998, and January 26, 1999.

These supplements provide for changes to the PRECAUTIONS, Carcinogenesis, Mutagenesis, and Impairment of Fertility and Pregnancy subsections, and to the OVERDOSAGE section, so that the dosage comparison between humans and animals is based on plasma drug concentrations rather than body surface area, as requested in our February 20, 1998, approval letter.

We have completed the review of these applications, as amended (package inserts submitted on January 26, 1999), and they are approved effective on the date of this letter with the revisions listed below.

Revise the following paragraph to read as follows.

PRECAUTIONS

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No evidence of tumorigenicity was seen in either a 2-year carcinogenicity study in Sprague Dawley rats, at oral (gavage) doses up to 200 mg/kg/day (estimated exposure was approximately 120 times the area under the plasma concentration versus time curve (AUC) for adults and children at the maximum recommended daily oral dose) or in a 92-week carcinogenicity study in mice at oral (gavage) doses up to 100 mg/kg/day (estimated exposure was approximately 45 times the AUC for adults and children at the maximum recommended daily oral dose).

These revisions are terms of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-829/S-001 and NDA 20-830/S-001." Approval of these submissions by FDA is not required before the labeling is used.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1084.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20830/S1

FINAL PRINTED LABELING

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

APPROVED
FEB 12 1999

9088802

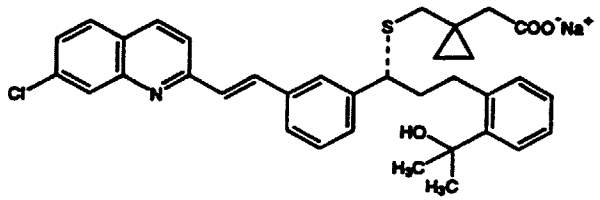
SINGULAIR®
(MONTELUKAST SODIUM)
TABLETS AND CHEWABLE TABLETS

DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR®, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Montelukast sodium is described chemically as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18. The structural formula is:



Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated SINGULAIR tablet contains 10.4 mg montelukast sodium, which is the molar equivalent to 10.0 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 methylcellulose, hydroxypropyl cellulose, titanium dioxide, red iron oxide, yellow iron oxide, and carnauba wax.

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: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene receptors (CysLT) found in the human airway. Cysteinyl leukotrienes and leukotriene receptor occupation have been correlated with the pathophysiology of asthma, including airway edema, 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 $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

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For the 5-mg chewable tablet, the mean C_{max} 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.

The comparative pharmacokinetics of montelukast when administered as two 5-mg chewable tablets versus one 10-mg film-coated tablet have not been evaluated.

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 distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. 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 (see *Drug Interactions*).

Elimination

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 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 (~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 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 cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast area under the plasma concentration curve (AUC) following a single 10-mg dose. The elimination of montelukast was slightly prolonged compared with that in healthy subjects (mean half-life, 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 hepatitis have not been evaluated.

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 administration of 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 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 at a dose of 10 mg once daily dosed to pharmacokinetic steady state:

- did not cause clinically significant changes in the kinetics of a single intravenous dose of theophylline (predominantly a cytochrome P450 1A2 substrate).

- did not change the pharmacokinetic profile of warfarin (a substrate of cytochromes P450 2A6 and 2C9) 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 (a substrate of cytochrome P450 3A4) or fexofenadine, 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 dosed 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 mcg.
- did not cause any clinically significant change in plasma profiles of prednisone or 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 SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12), SINGULAIR inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

The effect of SINGULAIR on eosinophils in the peripheral blood was examined in clinical trials in adults and pediatric asthmatic patients. SINGULAIR decreased mean peripheral blood eosinophils approximately 13 to 15% from baseline compared with placebo over the double-blind treatment periods. The relationship between this observation and the clinical benefits noted in the clinical trials is not known (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Clinical Studies

GENERAL

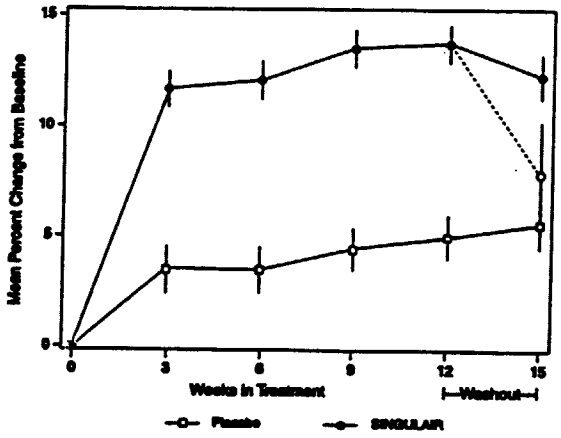
There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing. Although the pharmacokinetics of montelukast are similar whether dosed in the morning or the evening, efficacy was demonstrated in clinical trials in adults and pediatric patients in which montelukast was administered in the evening without regard to the time of food ingestion.

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 asthma 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.

The 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) similarly designed, randomized, 12-week, double-blind, placebo-controlled trials in 1576 patients (795 treated with SINGULAIR, 530 treated with placebo, and 251 treated with active control). The patients studied were mild and moderate, non-smoking asthmatics who required approximately 5 puffs of inhaled β-agonist per day on an "as-needed" basis. The patients had a mean baseline percent of predicted forced expiratory volume in 1 second (FEV_1) of 66% (approximate range, 40 to 90%). The co-primary endpoints in these trials were FEV_1 and daytime asthma symptoms. Secondary endpoints included morning and evening peak expiratory flow rates (AM PEFR, PM PEFR), rescue β-agonist requirements, nocturnal awakening 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, FEV_1, expressed as mean percent change from baseline, are shown in FIGURE 1.

FIGURE 1
FEV_1 Mean Percent Change from Baseline
(U.S. Trial)



The effect of SINGULAIR on other primary and secondary endpoints is shown in TABLE 1 as combined analyses of the U.S. and Multinational trials.

TABLE 1
Effect of SINGULAIR on Primary and Secondary Endpoints
in Placebo-controlled Trials
(Combined Analyses - U.S. and Multinational Trials)

	SINGULAIR		Placebo	
Endpoint	Baseline	Mean Change from Baseline	Baseline	Mean Change from Baseline
Daytime Asthma Symptom s (0 to 6 scale)	2.43	-0.45*	2.45	-0.22
β-agonist (puffs per day)	5.36	-1.56*	5.55	-0.41
AM PEFR (L/min)	361.3	24.5*	364.9	3.3
PM PEFR (L/min)	385.2	17.9*	389.3	2.0
Nocturnal Awakenings (#/week)	5.37	-1.84*	5.44	-0.79

* p<0.001, compared with placebo

In adult patients, SINGULAIR reduced "as-needed" β-agonist use by 26.1% from baseline compared with 4.6% for placebo. In patients with nocturnal awakenings of at least 2 nights per week, SINGULAIR reduced the nocturnal awakenings by 34% from baseline, compared with 15% for placebo (combined analysis).

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

TABLE 2
Effect of SINGULAIR on Asthma-Related Outcome Measurements
(Combined Analyses - U.S. and Multinational Trials)

	SINGULAIR	Placebo
Asthma Attack* (% of patients)	11.6†	18.4
Oral Corticosteroid Rescue (% of patients)	10.7†	17.5
Discontinuation Due to Asthma (% of patients)	1.4‡	4.0
Asthma Exacerbations **(% of days)	12.8†	20.5
Asthma Control Days*** (% of days)	38.5†	27.2
Physicians' Global Evaluation (score)§	1.77†	2.43
Patients' Global Evaluation (score)§§	1.60†	2.15
† p<0.001, compared with placebo ‡ p<0.01, compared with placebo		

* Asthma Attack defined as utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital; or treatment with oral, intravenous, or intramuscular corticosteroid.

** Asthma Exacerbation defined by specific clinically important decreases in PEFR, increase in β-agonist use, increases in day or nighttime symptoms, or the occurrence of an asthma attack.

*** An Asthma Control Day defined as a day without any of the following: nocturnal awakening, use of more than 2 puffs of β-agonist, or an asthma attack.

§ Physicians' evaluation of the patient's asthma, ranging from 0 to 6 ("very much better" through "very much worse," respectively).

§§ Patients' evaluation of asthma, ranging from 0 to 6 ("very much better" through "very much worse," respectively).

In one of these trials, a non-U.S. formulation of inhaled beclomethasone dipropionate dosed at 200 mcg (two puffs of 100 mcg ex-valve) twice daily with a spacer device was included as an active control. Over the 12-week treatment period, the mean percentage change in FEV_1 over baseline for SINGULAIR and beclomethasone were 7.49% vs 13.3% ($p<0.001$) respectively, see FIGURE 2; and the change in daytime symptom scores was -0.49 vs -0.70 on a 0 to 6 scale ($p<0.001$) for SINGULAIR and beclomethasone, respectively. The percentages of individual patients treated with SINGULAIR or beclomethasone achieving any given percentage change in FEV_1 from baseline are shown in FIGURE 3.

FIGURE 2
FEV_1
Mean Percent Change From Baseline
(Multinational Trial)

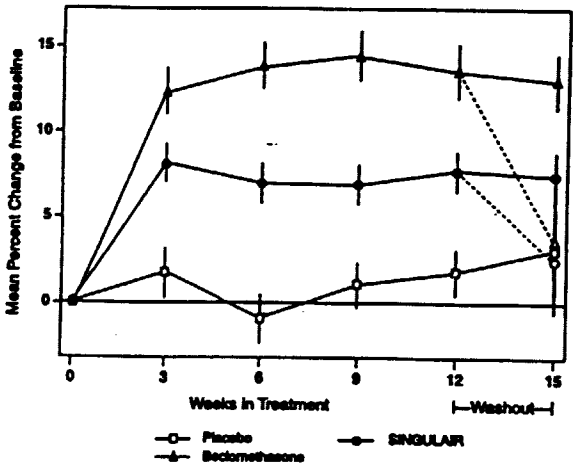
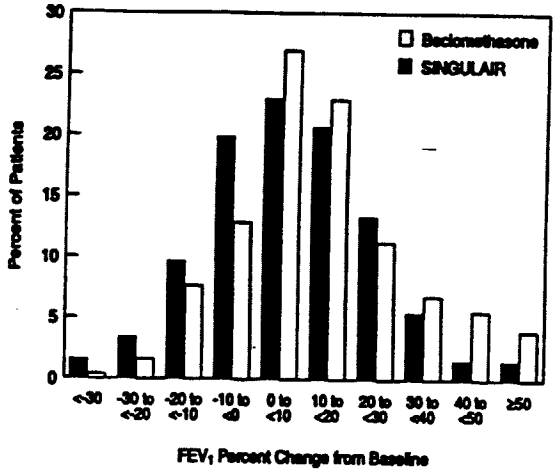


FIGURE 3
FEV_1
Distribution of Individual Patient Response
(Multinational Trial)



Onset of Action and Maintenance of Benefits

In each placebo-controlled trial in adults, the treatment effect of SINGULAIR, measured by daily diary card parameters, including symptom scores, "as-needed" β-agonist use, and PEFR measurements, was achieved after the first dose and was maintained throughout the dosing interval (24 hours). No significant change in treatment effect was observed during continuous once-daily evening administration in non-placebo-controlled extension trials for up to one year. Withdrawal of SINGULAIR in asthmatic patients after 12 weeks of continuous use did not cause rebound worsening of asthma.

PEDIATRIC PATIENTS 6 TO 14 YEARS OF AGE

The efficacy of SINGULAIR in pediatric patients 6 to 14 years of age was demonstrated in one 8-week double-blind, placebo-controlled trial in 336 patients (201 treated with SINGULAIR and 135 treated with placebo) using an inhaled β-agonist on an "as-needed" basis. The patients had a mean baseline percent predicted FEV_1 of 72% (approximate range, 45 to 90%) and a mean daily inhaled β-agonist requirement of 3.4 puffs of albuterol. Approximately 36% of the patients were on inhaled corticosteroids.

Compared with placebo, treatment with one 5-mg SINGULAIR chewable tablet daily, resulted in a significant improvement in mean morning FEV_1 percent change from baseline (8.7% in the group treated with SINGULAIR vs 4.2% change from baseline in the placebo group, $p<0.001$). There was a significant decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use (11.7% decrease from baseline in the group treated with SINGULAIR vs 8.2% increase from baseline in the placebo group, $p<0.05$). This effect represents a mean decrease from baseline of 0.56 and 0.23 puffs per day for the montelukast and placebo groups, respectively. Subgroup analyses indicated that younger pediatric patients aged 6 to 11 had efficacy results comparable to those of the older pediatric patients aged 12 to 14.

SINGULAIR, one 5-mg chewable tablet daily at bedtime, significantly decreased the percent of days asthma exacerbations occurred (SINGULAIR 20.6% vs placebo 25.7%, $p\leq0.05$). (See TABLE 2 for definition of asthma exacerbation.) Parents' global asthma evaluations (parental evaluations of the patients' asthma, see TABLE 2 for definition of score) were significantly better with SINGULAIR compared with placebo (SINGULAIR 1.34 vs placebo 1.69, $p\leq0.05$).

Similar to the adult studies, no significant change in the treatment effect was observed during continuous once-daily administration in one open-label extension trial without a concurrent placebo group for up to 6 months.

EFFECTS IN PATIENTS ON CONCOMITANT INHALED CORTICOSTEROIDS

Separate trials in adults evaluated the ability of SINGULAIR to add to the clinical effect of inhaled corticosteroids and to allow inhaled corticosteroid tapering when used concomitantly.

One randomized, placebo-controlled, parallel-group trial (n=226) enrolled stable asthmatic adults with a mean FEV_1 of approximately 84% of predicted who were previously maintained on various inhaled corticosteroids (delivered by metered-dose aerosol or dry powder inhalers). The types of inhaled corticosteroids and their mean baseline requirements included beclomethasone dipropionate (mean dose, 1203 mcg/day), triamcinolone acetonide (mean dose, 2004 mcg/day), flunisolide (mean dose, 1971 mcg/day), fluticasone propionate (mean dose, 1083 mcg/day), or budesonide (mean dose, 1192 mcg/day). Some of these inhaled corticosteroids were non-U.S.-approved formulations, and doses expressed may not be ex-actuator. The pre-study inhaled corticosteroid requirements were reduced by approximately 37% during a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose. Treatment with SINGULAIR resulted in a further 47% reduction in mean inhaled corticosteroid dose compared with a mean reduction of 30% in the placebo group over the 12-week active treatment period ($p\leq0.05$). Approximately 40% of the montelukast-treated patients and 29% of the placebo-treated patients could be tapered off inhaled corticosteroids and remained off inhaled corticosteroids at the conclusion of the study (p=NS). It is not known whether the results of this study are generalizable to asthmatics who require higher doses of inhaled corticosteroids or systemic corticosteroids.

In another randomized, placebo-controlled, parallel-group trial (n=642) in a similar population of adult patients previously maintained, but not adequately controlled, on inhaled corticosteroids (beclomethasone 336 mcg/day), the addition of SINGULAIR to beclomethasone resulted in statistically significant improvements in FEV_1 compared with those patients who were continued on beclomethasone alone or those patients who were withdrawn from beclomethasone and treated with montelukast or placebo alone over the last 10 weeks of the 16-week, blinded treatment period. Patients who were randomized to treatment arms containing beclomethasone had statistically significantly better asthma control than those

patients randomized to SINGULAIR alone or placebo alone as indicated by FEV_1, daytime asthma symptoms, PEFR, nocturnal awakenings due to asthma, and "as-needed" β-agonist requirements.

In adult asthmatic patients with documented aspirin sensitivity, nearly all of whom were receiving concomitant inhaled and/or oral corticosteroids, a 4-week randomized, parallel-group trial (n=80) demonstrated that SINGULAIR, compared with placebo, resulted in significant improvement in parameters of asthma control. The magnitude of effect of SINGULAIR in aspirin-sensitive patients was similar to the effect observed in the general population of asthmatic patients studied. The effect of SINGULAIR on the bronchoconstrictor response to aspirin or other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients has not been evaluated (see PRECAUTIONS, *General*).

EFFECTS ON EXERCISE-INDUCED BRONCHOCONSTRICTION (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 FEV_1 percent of predicted of 83% 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 FEV_1 and mean time to recovery to within 5% of the pre-exercise FEV_1. Exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose). This effect was maintained throughout the 12-week treatment period indicating that tolerance did not occur. SINGULAIR did not, however, prevent clinically significant deterioration in maximal percent fall in FEV_1 after exercise (i.e., ≥20% 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 effects similar to those observed in adults when exercise challenge 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 treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled β-agonists as prophylaxis and have available for rescue a short-acting inhaled β-agonist (see PRECAUTIONS, *General* and *Information for Patients*).

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

General

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

Patients should be advised to have appropriate rescue medication available. Therapy with SINGULAIR can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR should not be abruptly substituted for inhaled or oral corticosteroids.

SINGULAIR should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled β-agonists as prophylaxis and have available for rescue a short-acting inhaled β-agonist.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR. Although SINGULAIR is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Eosinophilic Conditions

In rare cases, patients on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established (see ADVERSE REACTIONS).

Information for Patients

- Patients should be advised to take SINGULAIR daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Patients should be advised that oral tablets of SINGULAIR are not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β-agonist medication available to treat asthma exacerbations.
- Patients should be advised that, while using SINGULAIR, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for 24-hour period are needed.
- Patients receiving SINGULAIR should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regimen of inhaled β-agonists as prophylaxis unless otherwise instructed by their physician. All patients should have available for rescue a short-acting inhaled β-agonist.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR.

Chewable Tablets

- *Phenylketonurics:* Phenylketonuric patients should be informed that the chewable tablet contains phenylalanine (a component of aspartame) 0.842 mg per 5-mg chewable tablet.

Drug Interactions

SINGULAIR has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin.

Although additional specific interaction studies were not performed, SINGULAIR was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Phenobarbital, which induces hepatic metabolism, decreased 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 cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in a 2-year carcinogenicity study in Sprague-Dawley rats at oral (gavage) doses up to 200 mg/kg/day using a diet- and dosing-optimized feeding regimen (estimated exposure was approximately 120 times the area under the plasma concentration versus time curve (AUC) for adults and children at the maximum recommended daily oral dose) or in a 92-week carcinogenicity study in mice at oral doses up to 100 mg/kg/day (estimated exposure was approximately 45 times the AUC for adults and children at the maximum recommended daily oral dose).

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an

oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

Pregnancy, Teratogenic Effects

Pregnancy Category B:

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (estimated exposure was approximately 100 times the AUC for adults at the maximum recommended daily oral dose) and in rabbits at oral doses up to 300 mg/kg/day (estimated exposure was approximately 110 times the AUC for adults at the maximum recommended daily oral dose). Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to SINGULAIR while pregnant. Healthcare providers are encouraged to report any prenatal exposure to SINGULAIR by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

Pediatric Use

The safety and effectiveness in pediatric patients below the age of 6 years have not been established. Long-term trials evaluating the effect of chronic administration of SINGULAIR on linear growth in pediatric patients have not been conducted.

Geriatric Use

Of the total number of subjects in clinical studies of montelukast, 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 responses 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

SINGULAIR 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 SINGULAIR 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:

Adverse Experiences Occurring in ≥1% of Patients with an Incidence Greater than that in Patients Treated with Placebo, Regardless of Causality Assessment

	SINGULAIR 10 mg/day (%) (n=1955)	Placebo (%) (n=1180)
Body As A Whole		
Asthenia/fatigue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Gastroenteritis, infectious	1.5	0.5
Pain, dental	1.7	1.0
Nervous System/Psychiatric		
Dizziness	1.9	1.4
Headache	18.4	18.1
Respiratory System Disorders		
Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/Skin Appendages Disorder		
Rash	1.6	1.2
*Laboratory Adverse Experiences**		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

* Number of patients tested (SINGULAIR and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

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

Cumulatively, 569 patients were treated with SINGULAIR for at least 6 months, 480 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

SINGULAIR has also been evaluated for safety in approximately 320 pediatric patients 6 to 14 years of age. Cumulatively, 169 pediatric patients were treated with SINGULAIR for at least 6 months, and 121 for one year or longer in clinical trials. The safety profile of SINGULAIR versus placebo in the double-blind, 8-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 SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: diarrhea, laryngitis, pharyngitis, nausea, otitis, sinusitis, and viral infection. The frequency of less common adverse events was comparable between SINGULAIR and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use: hypersensitivity reactions, including anaphylaxis, angioedema, pruritus, and urticaria.

In rare cases, patients on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established (see PRECAUTIONS, *Eosinophilic Conditions*).

OVERDOSAGE

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 340 times the AUC for adults and children at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 times the AUC for adults and children at the maximum recommended daily oral dose).

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week 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.

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 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and a silica gel desiccant canister

NDC 0006-0275-28 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, an 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, an 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 pack 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.

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued ~~November 1998~~
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20830/S1

PHARMACOLOGY REVIEW(S)

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Labeling Review

NDA No. 20-829/20-830 **Submission Date:** 19 MAR 98

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 12 JUN 98

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Merck Research Laboratories

Drug Name: *Generic:* montelukast sodium *Commercial:* Singulair™

The sponsor submitted draft labeling revisions for toxicology information in response to requests in the FDA approval letters for this drug (dated February 20, 1998). The revisions of the sponsor's human exposure ratios are based upon calculations by Dr. Shannon Williams (see attached Memorandum on Labeling revision for Carcinogenicity and Pregnancy sections). There are no substantial differences between the Sponsor's and Dr. Williams' versions of the label except in the impairment of fertility section. The AUC for fertility studies should be based on data from pregnant rats and from studies of comparable duration of administration. Thus, in agreement with the sponsor, the AUCs of 100 and 200 mg/kg should be based upon the toxicokinetic data from the pregnant rat study (TT #93-740-0). However, the AUC of 800 mg/kg should be based upon the 3-month studies (TT #92-0984-0 and TT #92-610-0), rather than on the 16-day study (TT #93-054-0), in rats. The following sections of the labeling should be revised as follows:

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no

effects on fertility in male rats at oral doses up to 800 mg/kg

Pregnancy
Pregnancy Category B:
No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (estimated exposure was approximately 90 times the AUC for adults at the maximum recommended daily oral dose) and in rabbits at oral doses up to 300 mg/kg/day (estimated exposure was approximately 110 times the AUC for adults at the maximum recommended daily oral dose). Montelukast crosses the placenta in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Nursing Mothers
Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

OVERDOSAGE
No mortality occurred following single oral doses up to 5000 mg/kg in mice (estimated exposure was approximately 340 times the AUC for adults and children at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 times the AUC for adults and children at the maximum recommended daily oral dose).
No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week 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.

RECOMMENDATION

1. The labeling revisions submitted by the sponsor are acceptable, with incorporation of the suggested revisions for the labeling sections entitled: Carcinogenesis, Mutagenesis, and Impairment of Fertility, Pregnancy Category, Nursing Mothers, and OVERDOSAGE as indicated above.

/S/ 6/12/98
Timothy J. McGovern, Ph.D., Pharmacologist

/S/ June 12, 1998

OCT - 9 1998

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Labeling Review #2

NDA No. 20-829/20-830 **Submission Date:** 20 AUG 98

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 09 OCT 98

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Merck Research Laboratories

Drug Name: *Generic:* montelukast sodium *Commercial:* Singulair™

The sponsor submitted a response to the Agency's approvable letter dated July 7, 1998. The approvable letter included modifications to the package circular on margins of safety based on systemic exposure data. In the current submission, the sponsor provided responses to requests from the Agency for changes to the PRECAUTIONS, "Carcinogenesis, Mutagenesis, and Impairment of Fertility" and "Pregnancy" subsections and to the OVERDOSAGE section. The sponsor agreed with most of the "fold" margins proposed by the Agency (see Labeling Review, 6/12/98) although they differed on the three exposure calculations which follow:

Based upon the above comments, the following sections of the labeling should read as follows:

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No evidence of tumorigenicity was seen in either a 2-year carcinogenicity study in Sprague Dawley rats, at oral (gavage) doses up to 200 mg/kg/day (estimated exposure was approximately 70 times the area under the plasma concentration versus time curve (AUC) for adults and children at the maximum recommended daily oral dose) or in a 92-week carcinogenicity study in mice at oral (gavage) doses up to 100 mg/kg/day (estimated exposure was approximately 45 times the AUC for adults and children at the maximum recommended daily oral dose).

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

Pregnancy
Pregnancy Category B:
No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (estimated exposure was approximately 100 times the AUC for adults at the maximum recommended daily oral dose) and in rabbits at oral doses up to 300 mg/kg/day (estimated exposure was approximately 110 times the AUC for adults at the maximum recommended daily oral dose). Montelukast crosses the placenta in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Nursing Mothers
Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

OVERDOSAGE
No mortality occurred following single oral doses up to 5000 mg/kg in mice (estimated exposure was approximately 340 times the AUC for adults and children at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 times the AUC for adults and children at the maximum recommended daily oral dose).
No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week 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.

RECOMMENDATIONS

1. The exposure ratio for the 2-year rat carcinogenicity study at doses up to 200 mg/kg/day should remain fold.

2. Labeling revisions of exposure ratios for the male rat fertility study and the rat teratogenicity study are required due to differences in diet administration among various studies. While, the proposed exposure-ratio submitted by the sponsor (100-fold) in their response to FDA comment #3 is acceptable, the revised exposure-ratio (160-fold) for comment #2 falls between the previous Agency recommendation (110-fold) and that proposed by the sponsor (180-fold). Thus, the labeling is acceptable, with incorporation of the suggested revisions for the labeling sections entitled: Carcinogenesis, Mutagenesis, and Impairment of Fertility, and Pregnancy Category as indicated above.

/S/ 10/9/98

Timothy J. McGovern, Ph.D., Pharmacologist

/S/

Oct. 9, 1998

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HFD-570/ C.J. Sun
HFD-570/ A. Trontell
HFD-570/ D. Hilfiker
HFD-570/T.J. McGovern

DIVISION OF PULMONARY DRUG PRODUCTS
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Addendum to Labeling Review #2

NDA No. 20-829/20-830 **Submission Date:** 20 AUG 98

Reviewer: Timothy J. McGovern, Ph.D. **Review Completed:** 07 DEC 98

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Merck Research Laboratories

Drug Name: *Generic:* montelukast sodium *Commercial:* Singulair™

The sponsor submitted a response to the Agency's approvable letter dated July 7, 1998 which was reviewed in Labeling Review #2 (10/9/98). A teleconference was subsequently held with the sponsor on 11/17/98 (see minutes) to discuss issues raised in the review. Briefly, both parties agreed with the AUC exposure ratios recommended in Items 2 and 3 of Labeling Review #2 concerning fertility effects in male rats and teratogenicity in rats. However, the sponsor disagreed with the recommendation in Item 1 concerning the estimated exposure ratio in a 2-year rat carcinogenicity study. The sponsor proposed that oral (gavage) doses up to 200 mg/kg/day approximate an estimated exposure ratio of 120 times the AUC for adults and children, rather than the 70-fold ratio recommended by the Agency. The 120-fold ratio is based on AUC values from one arm of a 16-day oral study (TT #93-054-0) in which systemic exposure was increased by dosing animals 4 hours prior to feeding, a unique regimen also employed in the rat carcinogenicity study (TT #93-078-0). The Agency agreed that this dosing regimen is more appropriate for determination of exposure levels in the carcinogenicity study. However, the study duration was considered to be inadequate for determination of systemic exposure for chronic studies since the enzyme-induction potential of long-term drug treatment is currently unknown, although a previous 4-day oral administration study in rats demonstrated an absence of drug-induced enzyme induction. The sponsor indicated that the 16-day oral gavage study included two arms, one in which animals were fed 2 hours pre-dosing and the other in which animals were fed 4 hours post-dosing. The sponsor noted that exposure levels following dosing with 200 mg/kg in the "feeding prior to dosing arm" were similar to exposure levels observed in two 3-month studies (Study Nos. TT #92-098-0 and TT #92-610-0) at the same dose in which animals were fed ad libitum, indicating that enzyme induction was not a factor.

The systemic exposure to DMP 777 (expressed as AUC, μM.hr, following oral (gavage) administration) from relevant studies is summarized below:

			Males		
Study #:	TT #92-031-0	T93-054-0	T93-054-0	T92-610-0	T92-098-0
Duration:	1-day	16-day	16-day	14 wk	14 wk
Feed. Regimen:	unknown	fed 2 hrs pre-dose	fed 4 hrs post-dose	ad libitum	free access
Dose (mg/kg)					
50	25.18	22.78	55.78	58.5	
200	213.97	141.24	404.75	200.2	173.4
400	271.02	229.67	448.02	255.1	276.4
800	771.86	294.05	486.05	415.5	262

			Females		
Study #:	TT #92-031-0	T93-054-0	T93-054-0	T92-610-0	T92-098-0
Duration:	1-day	16-day	16-day	14 wk	14 wk
Feed. Regimen:	unknown	fed 2 hrs pre-dose	fed 4 hrs post-dose	ad libitum	free access
Dose (mg/kg)					
50	34.7	28.5	34.24	37.9	
200	126.8	167.44	248.86	215.2	162.5
400	212.1	245.76	278	275.7	135.8
800	461.09	176.57	229.68	380.6	157.4

The above table shows that similar exposure levels are observed when similar feeding regimens are utilized regardless of dosing duration. However, exposure levels are increased when food is withheld until 4 hours after dosing. Thus, the Agency accepts the sponsor's use of the AUC values from the arm of the 16-day oral study, in which systemic exposure was increased by dosing animals 4 hours prior to feeding, to determine the exposure fold ratio in the rat carcinogenicity study which utilized the same dosing/feeding regimen.

Therefore, the current labeling should state that the mean AUC at 200 mg/kg/day in the rat carcinogenicity study provides a 120-fold AUC ratio compared to adults and children. In addition, a statement indicating the increased systemic exposure resulting from the unique dosing/feeding regimen utilized in this study should be included since the exposure ratio at 200 mg/kg for the carcinogenicity study is greater than the resulting exposure ratios at greater doses in studies utilizing ad libitum feeding regimens.

Based upon the above comments, the following section of the labeling should read as follows with revised portions in bold lettering:

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No evidence of tumorigenicity was seen in either a 2-year carcinogenicity study in Sprague Dawley rats, at oral (gavage **with a unique dosing regimen**) doses up to 200 mg/kg/day (estimated exposure was approximately **120** times the area under the plasma concentration versus

time curve (AUC) for adults and children at the maximum recommended daily oral dose), or in a 92-week carcinogenicity study in mice at oral (gavage) doses up to 100 mg/kg/day (estimated exposure was approximately 45 times the AUC for adults and children at the maximum recommended daily oral dose).

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

RECOMMENDATIONS

1. The exposure ratio for the 2-year rat carcinogenicity study at doses up to 200 mg/kg/day should be increased fold. In addition, a statement indicating the increased systemic exposure resulting from the unique dosing/feeding regimen utilized in this study should be included since the exposure ratio at 200 mg/kg for the carcinogenicity study is greater than the resulting exposure ratios at greater doses in studies utilizing ad libitum feeding regimens.

/S/

12/7/98

Timothy J. McGovern, Ph.D., Pharmacologist

/S/ Dec. 7, 1998

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HFD-570/T.J. McGovern

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20830/S1

ADMINISTRATIVE DOCUMENTS

FDA

MEMORANDUM

FROM: Shannon Williams. Ph.D. Pharmacologist

TO: NDA 20-829 and 20-830

DATE: February 27. 1998

RE: Labeling revision for Carcinogenicity and Pregnancy sections.

Background: In the Approval letters for NDA-20-829 and 20-830, dated 02 Feb 98. the Sponsor was asked to submit a labeling supplement revising, the PRECAUTIONS. Carcinogenesis. Mutagenesis, and Impairment of Fertility and Pregnancy subsections and OVERDOSAGE section so that dosage comparison between humans and animals is based on plasma drug concentrations, rather that body surface area. Thus, the purpose of this memorandum was to provide a revised labeling of the said sections based on available data submitted in both NDA applications.

Clinical PK data from Repeat dose studies in adult patients (Report Nos. 026 and 036) showed mean AUC values in adults of 2.67 ug·hr/ml following repeated dose adminsitration of a 10.0 mg/day dose. In pediatrics, single dose adminsitration of a 5 mg dose resulted in similar AUC values of 2.928 ug·hr/ml. Table 1 Below presents AUC values from repeat dose studies conducted in mice, rats, and rabbits.

Study No.	Duration/route	Species	Dose (mg/kg)	AUC (ug·hr/ml)	Ratio to Human Exposure[5]
TT #93-034-0	4-wk/gavage	mice	100	116.7[1]	43.7X
			800-1200	567.23[1]	212.4
TT #92-113-0	Single dose gavage	mice	800	901.7[2]	337.7X
TT #92-610-0	3-month/gavage	rats	100	108.6[3]	40.7X
TT#92-098-0	3-month/gavage		200	187.8.[4]	70.3X
			400	235.8[4]	88.3X
			800	303.9[4]	113.8X
TT #92-031-0	Single dose gavage	rats	800	616.5[5]	230.9X
TT#93-738-0	Gestation D18	Rabbits	300	291.8[6]	109.3X

1. Doses extrapolated from linear section of dose response curve (50-400 mg/kg using both sexes; Pharmacol. Review #8, dated 02 JUN 1997).
2. AUC values plateaued in mice at a dose of 800 mg/kg following single dose administration (Pharmacol. Review #8. dated 02 JUN 1997)
3. AUC values for the 100 mg/kg dose were extrapolated from linear section of dose response curve generated using data from both sexes and both studies over the dose range of 50-400 mg/kg (Pharmacol. Review #7, dated 24 OCT 1996).
4. AUC values represent the means actual values in rats of both sexes from both studies at the 200. 400 and 800 mg/kg doses (Pharmacol. Review #8. dated 02 JUN 1997).
5. AUC values plateaued in rats at a dose of 800 mg/kg following single dose administration in rats (Pharmacol. Review #8. dated 02 JUN 1997)
6. AUC values at the end of dosing gestation Days 6-18 in rabbits (Pharmacol. Review #8. dated 02 JUN 1997)
7. Since exposure (AUC values) in adults and humans were nearly equivalent. ratios to human exposures are based on exposure (AUC) values in adults. e.g. 2.67 ug·hr/ml following a maximum daily dose of 10 mg.

Suggested labeling revisions are indicated below:

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assays, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assays in Chinese hamster ovary cells, and in the in vivo mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 40 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg

Pregnancy

Pregnancy Category B:

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (estimated exposure was approximately 90 times the AUC for adults at the maximum recommended daily oral dose) and in rabbits at oral doses up to 300 mg/kg/day (estimated exposure was approximately 110 times the AUC for adults at the maximum recommended daily oral dose). Montelukast crosses the placenta in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies in rats have shown that montelukast is excreted in milk. It is not known if monteluksat is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

OVERDOSAGE

No mortality occurred following single oral doses up to 5000 mg/kg in mice (estimated exposure was approximately 340 times the AUC for adults and children at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 times the AUC for adults and children at the maximum recommended daily oral dose).

Memo to file: NDA 20829, 20830
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No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week 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

Note: Ratios expressed for exposure in rats are based on mean AUC values

/S/ 2/27/98

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c.c. HFD-570
HFD-570/C.J.Sun
HFD-570/P. Honig
HFD-570/S. Williams
HFD-570/B. Kuzmik