SINGULAIR™

(montelukast sodium)

I. THERAPEUTIC CLASS

SINGULAIR™ (montelukast sodium) is a selective and orally active leukotriene receptor antagonist that specifically inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

II. INDICATIONS

SINGULAIR is indicated in adults for the prophylaxis and chronic treatment of asthma, including the prevention of exercise-induced bronchoconstriction.

III. DOSAGE AND ADMINISTRATION

Asthma

Singulair should be taken once daily in the evening (one-10 mg tablet)

Exercise-Induced Bronchocontriction (EIB)

For prevention of EIB, a single dose (one-10mg tablet) of SINGULAIR should be taken at least 2 hours before exercise.

An additional dose of SINGULAIR should not be taken within 24 hours of previous dose. Patients already taking SINGULAIR daily for another indication (including chronic asthma) should not take an additional dose to prevent EIB. All patients should have available for rescue a short-acting β - agonist.

IV. CONTRAINDICATIONS

Hypersensitivity to any component of this product

V. PRECAUTIONS

The efficacy of oral SINGULAIR for the treatment of acute asthma attacks has not been established. Therefore, oral SINGULAIR should not be used to treat acute asthma attacks.

Patients should be advised to have appropriate rescue medication available.

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

Neuropsychiatric events have been reported in patients taking SINGULAIR (see SIDE EFFECTS). Since other factors may have contributed to these events, it is not known if they are related to SINGULAIR. Physicians should discuss these adverse experiences with their patients and/or caregivers. Patients and/or caregivers should be instructed to notify their physician if these changes occur.

In rare cases patients receiving anti-asthma agents, including leukotriene receptor antagonists, have experienced one or more of the following: eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy sometimes diagnosed as Churg-Strauss syndrome, a systemic eosinophilic vasculitis. These cases have been sometimes associated with the reduction or withdrawal of oral corticosteroid therapy. Although a causal relationship with leukotriene receptor antagonism has not been established, caution and appropriate clinical monitoring are recommended in patients receiving SINGULAIR.

Singulair should not be used as monotheraphy for the treatment and management of exerciseinduced bronchospasm. Patients who have exacerbations of asthma after exercise should continues to use their usual regimen of inhaled-agonist as prophylaxis and have available for rescue a short-acting inhaled-agonist.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steoridal antiinflamatory agent 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 NSAIDs in aspirin-sensitive asthmatic patients.

VI. PREGNANCY

SINGULAIR should be used during pregnancy only if clearly needed.

Available data from published prospective and retrospective cohort studies with montelukast use in pregnant women evaluating major birth defects have not established a drug-associated risk. Available studies have methodologic limitations, including small sample size, in some cases retrospective data collection, and inconsistent comparator groups.

VII. NURSING MOTHERS

It is not known if SINGULAIR 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.

VIII. PEDIATRIC USE

SINGULAIR 10 mg tablets should not be prescribed to patients <15 years of age.

IX. USE IN THE ELDERLY

In clinical studies, there were no age-related differences in the efficacy or safety profiles of SINGULAIR.

X. DRUG INTERACTIONS

SINGULAIR may be administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma. In drug-interactions 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 (ethinyl estradiol/norethindrone 35/1), terfenadine, digoxin and warfarin.

The area under the plasma concentration-time curve (AUC) for montelukast was decreased approximately 40% in subjects with co-administration of phenobarbital. No dosage adjustment for SINGULAIR is recommended.

In vitro studies have shown that montelukast is an inhibitor of CYP 2C8. However, data from a clinical drug-drug interaction study involving montelukast and rosiglitazone (a probe substrate representative of drugs primarily metabolized by CYP2C8) demonstrated that montelukast does not inhibit CYP2C8 in vivo. Therefore, montelukast is not anticipated to alter the metabolism of drugs metabolized by this enzyme (e.g. paclitaxel, rosiglitazone, and repaglinide.)

In vitro studies have shown that montelukast is a substrate of CYP 2C8, 2C9, and 3A4. Data from a clinical drug-drug interaction study involving montelukast and gemfibrozil (an inhibitor of both

CYP 2C8 and 2C9) demonstrated that gemfibrozil increased the systemic exposure of montelukast by 4.4-fold. Co-administration of itraconazole, a strong CYP 3A4 inhibitor, with gemfibrozil and montelukast did not further increase the systemic exposure of montelukast. The effect of gemfibrozil on systemic exposure of montelukast is not considered to be clinically meaningful based on clinical safety data with doses greater than the 10 mg approved dose in adults (e.g., 200 mg/day to adult patients for 22 weeks, and up to 900 mg/day to patients for approximately one week) where clinically important adverse experiences were not observed. Therefore, no dosage adjustment of montelukast is required upon co-administration with gemfibrozil. Based on in vitro data, clinically important drug interactions with other known inhibitors of CYP 2C8 (e.g., trimethoprim) are not anticipated. In addition, co-administration of montelukast with itraconazole alone resulted in no significant increase in the systemic exposure of montelukast.

XI. SIDE EFFECTS

SINGULAIR has been generally well tolerated. Side effects, which usually were mild, generally did not require discontinuation of therapy. The overall incidence of side effects reported with SINGULAIR was comparable to placebo.

Adults 15 Years of Age and Older

SINGULAIR has been evaluated in approximately 2600 adult patients 15 years of age and older in clinical studies. In two similarly designed, 12-week placebo-controlled clinical studies, the only adverse experiences reported as drug related in ≥ 1% of patients treated with SINGULAIR and at a greater incidence than in patients treated with placebo were abdominal pain and headache. The incidences of these events were not significantly different in the two treatment groups.

Cumulatively, 544 patients were treated with SINGULAIR for at least 6 months, 253 for one year and 21 for 2 years in clinical studies. With prolonged treatment, the adverse experience profile did not change.

The safety profile of SINGULAIR when administered as a single dose for prevention of EIB in adult and adolescent patients 15 years of age and older was consistent with the safety profile previously described for SINGULAIR.

Postmarketing Experience

System Organ Class	Adverse Experience Term	Frequency Category*

Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
	thrombocytopenia	Very rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare

Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness tremor§)	Uncommon
	disturbance in attention, memory impairment	Rare
	hallucinations, disorientation, suicidal thinking and behaviour (suicidality), tic, obsessive-compulsive symptoms, dysphemia	Very Rare
Nervous system disorder	dizziness, drowsiness paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS), pulmonary eosinophilia	Very Rare
Gastrointestinal disorders	diarrhoea€, nausea€, vomiting€	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common

	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash€	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
Renal and urinary disorders	Enuresis in children	Uncommon
General disorders and administration site conditions	pyrexia€	Common
	asthenia/fatigue, malaise, oedema,	Uncommon

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥ 1 /1 0), Common (≥ 11100 to <1/10), Uncommon (≥ 1 / 1000 to <1/100), Rare (≥ 1/10,000 to <1/1000), Very Rare (<1/10,000).

† This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.

€ This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.

§Frequency Category: Rare

XII. OVERDOSAGE

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, SINGULAIR has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short-term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdosage in postmarketing experience and clinical studies with SINGULAIR. These include reports in adults and children with a dose as high as 1000 mg. The clinical and laboratory findings observed were consistent with the safety profile in adults and pediatric patients. There were no adverse experiences in the majority of overdosage reports. The most frequently occurring adverse experiences were consistent with the safety profile of

SINGULAIR and included abdominal pain, somnolence, thirst, headache, vomiting, and psychomotor hyperactivity.

It is not known whether montelukast is dialyzable by peritoneal- or hemodialysis.

XIII. CLINICAL PHARMACOLOGY

XIIIa. Mechanism of Action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4), are potent inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors . The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma. In asthma, leukotrienemediated effects include a number of airway actions, including bronchoconstriction, mucous secretion, vascular permeability, and eosinophil recruitment.

Montelukast is orally active compound that significantly improves parameters of asthmatic inflammation. Based on biochemical and pharmacological bioassays, it 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 potently inhibits physiologic actions of LTC_4, LTD_4, and LTE_4 at the $CysLT_1$ receptor without any agonist activity.

XIIIb. Pharmacokinetics

Absorption

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

Safety and efficacy were demonstrated in clinical studies where the 10-mg film-coated tablet was administered 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 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 .

In vitro studies using human liver microsomes indicate that cytochrome P450 3A4, 2C8, 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.

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 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. No difference in pharmacokinetics was noted between dosing in the morning or in the evening. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (~14%).

Characteristics in Patients

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. In clinical studies, there do not appear to be any differences in clinically important effects.

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 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. 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

The plasma concentration profile of montelukast following administration of the 10-mg filmcoated tablet is similar in adolescents ≥15 years old and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years old.

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 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 SINGULAIR is recommended (see PRECAUTIONS).

XIIIc. Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatic patients. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction.

Montelukast causes bronchodilation within 2 hours of oral administration; these effects were additive to the bronchodilation caused by a β-agonist.

Clinical studies in 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 studies 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.

XIIId. Clinical Studies

ADULTS 15 YEARS OF AGE AND OLDER

The efficacy of SINGULAIR for the chronic treatment of asthma in adults 15 years of age and older was demonstrated in two (US and Multinational) similarly designed 12-week double-blind, placebo-controlled studies in 1325 patients (795 treated with SINGULAIR and 530 treated with placebo). Patients were symptomatic and using approximately 5 puffs of β-agonist per day on an "as-needed" basis. The mean baseline percent of predicted forced expiratory volume in 1 second (FEV_1) was 66% (approximate range, 40 to 90%). In these studies, asthma symptoms, asthma-related outcomes, respiratory function, and "as-needed" β-agonist use were measured. Endpoints were analyzed in each study and in a combined analysis according to a prespecified data analysis plan. The following clinical results were observed:

Asthma Symptoms and Asthma-related Outcomes

SINGULAIR, 10 mg once daily in the evening, significantly improved measurements of patientreported daytime symptoms and nighttime awakenings in each study and in the combined analysis, compared with placebo. In patients with nocturnal awakenings of at least 2 nights per week, SINGULAIR reduced the nocturnal awakenings by 34% from baseline, significantly better than the reduction of 14% for the placebo group (combined analysis).

SINGULAIR, compared with placebo, significantly improved asthma-related outcome measurements. In the combined analysis, SINGULAIR, compared with placebo, decreased asthma attacks by 37%, corticosteroid rescue by 39%, discontinuations due to worsening asthma by 65%, asthma exacerbations by 38% and increased asthma-free days by 42%.

Physicians' and patients' global asthma evaluations and asthma-specific quality-of-life evaluations (in all domains, including normal daily activity and asthma symptoms) were significantly better with SINGULAIR compared with placebo in each study and in the combined analysis.

Respiratory Function

Compared with placebo, SINGULAIR caused significant improvements in parameters of respiratory function (FEV_1 and peak expiratory flow rate, PEFR) in each study and in the combined analysis:

Effect of SINGULAIR, 10 mg Daily, on Parameters of Respiratory Function in Adults 15 Years and Older (Combined Analysis)

	SINGULAIR n=795	Placebo n=530
Morning FEV_1 (% change from baseline)	10.4*	2.7
AM PEFR (L/min change from baseline)	24.5*	3.3
PM PEFR (L/min change from baseline)	17.9*	2.0

* Significantly better than placebo ($p \leq 0.001$)

β-agonist Use

Compared with placebo, SINGULAIR significantly decreased the use of "as-needed" β-agonist by 26.1% from baseline compared with 4.6% in the placebo group in the combined analysis. The decreases were also significant in each of the studies ($p \leq 0.001$).

Onset of Action and Maintenance of Benefits

In each study and in the combined analysis, 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). Treatment effect also remained constant during continuous once-daily administration in extension studies for up to one year. Withdrawal of SINGULAIR in asthmatic patients after 12 weeks of continuous use did not cause rebound worsening of asthma. (See also EFFECTS ON EXERCISE-INDUCED BRONCHOCONSTRICTION.)

Effects Relative to Inhaled Corticosteroids

In one of the two 12-week double-blind studies in adults (Multinational), SINGULAIR was compared with inhaled beclomethasone (200 µg twice daily with a spacer device). SINGULAIR demonstrated a more rapid initial response, although over the full duration of the study beclomethasone provided a greater average treatment effect. However, a high percent of patients treated with SINGULAIR achieved similar clinical responses compared with inhaled beclomethasone.

EFFECTS ON EXERCISE-INDUCED BRONCHOCONSTRICTION

The efficacy of SINGULAIR, 10 mg, when given as a single dose 2 hours before exercise for the prevention of EIB was investigated in three (U.S. and Multinational), randomized, doubleblind, placebo-controlled crossover studies that included a total of 160 adult and adolescent patients 15 years of age and older with EIB. Exercise challenge testing was conducted at 2 hours, 8.5 or 12 hours, and 24 hours following administration of a single dose of study drug (SINGULAIR 10 mg or placebo). The primary endpoint was the mean maximum percent fall in FEV_1 following the 2 hours post-dose exercise challenge in all three studies (Study A, Study B, and Study C). In Study A, a single dose of SINGULAIR 10 mg demonstrated a statistically significant protective benefit against EIB when taken 2 hours prior to exercise. Some patients were protected from EIB at 8.5 and 24 hours after administration; however, some patients were not. The results for the mean maximum percent fall at each timepoint in Study A are shown in TABLE 3 and are representative of the results from the other two studies.

Mean Maximum Percent Fall in FEV_1 Following Exercise Challenge in Study A (N=47) ANOVA Model

Time of exercise challenge following medication administration	Mean Maximum percent fall in FEV_1*		Treatment difference % for SINGULAIR versus Placebo (95% CI)*
	SINGULAIR	Placebo	
2 hours	13	22	-9 (-12, -5)
8.5 hours	12	17	-5 (-9, -2)
24 hours	10	14	-4 (-7, -1)

*Least squares-mean

In a 12-week, randomized, double-blind, parallel group study of 110 adult and adolescent 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 preexercise 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.

EFFECTS ON ASTHMATIC INFLAMMATION

Several studies have shown SINGULAIR inhibits parameters of asthmatic inflammation. In a placebo-controlled crossover study (n=12), SINGULAIR inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75 and 57%, respectively.

Because inflammatory cell (eosinophil) infiltration is an important feature of asthma, the effects of SINGULAIR on eosinophils in the peripheral blood and airway were examined. In Phase IIb/III clinical studies in adults, SINGULAIR significantly decreased peripheral blood eosinophils approximately 15% from baseline, compared with placebo.
In a 4-week, randomized, parallel group study (n=40) in adults, SINGULAIR significantly decreased airway eosinophils (as assessed in sputum) by 48% from baseline compared with an increase of 23% from baseline with placebo. In this study, peripheral blood eosinophils significantly decreased, and clinical asthma endpoints improved with treatment with SINGULAIR.

XIV. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence that SINGULAIR affects the ability to drive and use machines.

XV. ANIMAL TOXICOLOGY

Acute Toxicity

No mortality occurred following a single oral administration of montelukast sodium at doses up to 5000 mg/kg, in mice and rats, (15,000 mg/m^2 and 29,500 mg/m^2 in mice and rats, respectively) the maximum dose tested (oral LD_{50} >5000 mg/kg). This dose is equivalent to 25,000 times the recommended daily adult human dose*.

Chronic Toxicity

*Based on an adult patient weight of 50 kg.

The toxic potential of montelukast sodium was evaluated in a series of repeated dose toxicity studies of up to 53 weeks in monkeys and rats and up to 14 weeks in infant monkeys and in mice.

Montelukast sodium was well tolerated at doses which provide a wide margin of safety based on total dose administered. The no effect level for all toxicological parameters in any of the species tested was at least 125 times the recommended human dose*. There were no findings that would preclude administration at the therapeutic dosage level for both adults and pediatric patients.

Carcinogenicity

Montelukast sodium was not carcinogenic when administered at oral doses of up to 200 mg/kg/day in a 106-week study in rats, or at oral doses of up to 100 mg/kg/day in a 92-week study in mice. These doses are equivalent to 1000 times and 500 times the recommended adult human dose*.

Mutagenesis

Montelukast sodium was found to be neither genotoxic nor mutagenic. Montelukast sodium was negative in the in vitro microbial mutagenesis assay and the V-79 mammalian cell mutagenesis assays, with and without metabolic activation. There was no evidence of genotoxicity in the in vitro alkaline elution assay in rat hepatocytes and the in vitro chromosomal aberration assays in Chinese hamster ovary cells, with or without a microsomal enzyme activation system. Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of oral doses of up to 1200 mg/kg (3600 mg/m^2) (6000 times the recommended daily adult dose*).

Reproduction

Fertility and reproductive performance were not affected in studies with male rats given oral doses of up to 800 mg/kg/day or with female rats given doses of up to 100 mg/kg/day. These dosages provide margins of 4000-fold and 500-fold, respectively, above the recommended adult human dose*.

Development

*Based on an adult patient weight of 50 kg.

In developmental toxicity studies, there were no treatment related adverse effects at doses up to 400 mg/kg/day in rats and up to 100 mg/kg/day in rabbits. Fetal exposure of montelukast sodium in rats and rabbits does occur and significant concentrations of drug were observed in milk of lactating rats.

If there is any adverse events please inform to PT Organon Pharma Indonesia Tbk, Jakarta. Telephone : (021) 31107001; Email : dpoc.indonesia@organon.com

HARUS DENGAN RESEP DOKTER

Storage condition:

Store below 30°C

Protect from moisture and light.

Presentation:

Singulair 10 mg film-coated tablet; Box, 4 blisters @ 7 tablets, Reg. No. DKL2006609717A1

Manufactured by:

Organon Pharma (UK) Limited

Cramlington, Northumberland NE23 3JU, United Kingdom

Registered and packed by:

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

S-WPC-MK0476-MF-062018, S-WPC-MK0476-MF-112018 & S-WPC-MK0476-MF-052019

PI Version 4

ORGANON

INFORMASI MENGENAI SINGULAIR™ UNTUK PASIEN

Harap baca leaflet ini dengan seksama sebelum anda mulai minum obat ini, walau anda telah menggunakan obat ini sebelumnya. Beberapa informasi dalam leaflet sebelumnya dapat berubah.
Ingatlah bahwa dokter anda meresepkan obat ini hanya untuk anda. Jangan berikan kepada orang lain.

Apakah SINGULAIR™ ?

SINGULAIR (montelukast sodium) mengandung bahan aktif natrium montelukast. Setiap tablet 10-mg mengandung montelukast 10 mg.
SINGULAIR adalah antagonis reseptor leukotrien yang menghambat substansi yang disebut leukotrien. Leukotrien menyebabkan menyempitnya dan membengkaknya saluran napas pada paru anda. Penghambatan leukotrien memperbaiki gejala asma dan membantu mencegah serangan asma.

Didaftarkan oleh:

PT Organon Pharma Indonesia Tbk
Pasuruan, Jawa Timur

Mengapa dokter saya meresepkan SINGULAIR?

Dokter anda meresepkan SINGULAIR untuk mengobati:
Singulair diindikasikan pada orang dewasa untuk profilaksis dan pengobatan kronis asma, termasuk pencegahan bronkokonstriksi akibat olahraga.

Apakah asma?

Asma adalah penyakit paru kronik. Asma tidak dapat disembuhkan – tetapi dapat dikontrol.
Karakteristik asma adalah:

- Saluran napas menyempit menyebabkan sulit bernapas. Penyempitan ini memburuk dan membaik bergantung respons terhadap berbagai kondisi.

- Inflamasi saluran napas; yaitu dinding saluran napas membengkak.
- Saluran napas sensitif yang memberikan reaksi terhadap berbagai hal, seperti asap rokok, serbuk sari bunga atau udara dingin.

Gejala asma adalah:

Batuk, bersin dan sesak napas. Tidak semua orang mengalami mengi asma. Pada beberapa orang, gejala asma yang timbul hanya batuk. Gejala sering terjadi pada malam hari atau setelah berolah raga.

Apakah asma terinduksi olah raga?

Asma terinduksi olah raga, yang lebih tepat disebut bronkokonstriksi terinduksi olah raga yang terjadi ketika olah raga memicu gejala asma.

Bagaimana saya mengetahui bahwa saya memiliki asma ?

Dokter anda akan menentukan apakah anda memiliki asma berdasarkan gejala yang anda alami dan/atau seberapa baik anda dapat bernapas mengeluarkan udara masuk dan keluar dari paru. Dokter anda dapat menggunakan alat yang disebut alat pengukur arus puncak/*peak flow meter* atau spirometer untuk menguji fungsi paru anda.

Pengobatan dapat mengontrol asma. Penting untuk mengobati asma walau gejalanya ringan sehingga anda dapat mencegah memberatnya asma.

Bagaimanakah mengobati asma?

Untuk membantu mencegah gejala asma dan memperbaiki napas anda maka anda sebaiknya bekerjasama dengan dokter untuk:

- Merencanakan cara mencegah atau mengurangi kontak dengan kondisi yang dapat memicu episode asma (contohnya, merokok termasuk perokok sekunder, tungau debu, kecoa, jamur, serbuk sari bunga, bulu hewan, perubahan udara dan suhu dan infeksi saluran napas atas, seperti flu).
- Mengembangkan rencana pengobatan yang terbaik untuk mengontrol asma anda.

Bagaimana SINGULAIR mengobati asma?

SINGULAIR menghambat substansi dalam paru anda yang disebut leukotrien yang menyebabkan penyempitan dan inflamasi saluran napas.

Mengapa kepatuhan (minum obat sesuai resep) adalah penting?

Minum obat anda sesuai dengan instruksi dokter atau penyedia layanan kesehatan akan dapat membantu mengurangi beratnya asma anda dan frekuensi serangan asma anda.

Apakah yang harus saya ketahui sebelum dan ketika minum SINGULAIR?

Penting bagi anda untuk melanjutkan minum SINGULAIR setiap hari sesuai resep dokter, bahkan ketika anda tidak mengalami gejala, atau bila anda anda mengalami serangan asma.

Bila gejala asma anda memberat, maka anda harus segera menghubungi dokter anda.

SINGULAIR tidak untuk mengobati serangan asma akut. Bila terjadi serangan, anda harus mengikuti instruksi yang diberikan oleh dokter anda untuk keadaan tersebut.

Perubahan perilaku dan mood dilaporkan terjadi pada pasien yang minum SINGULAIR. Bila anda anda mengalami perubahan ini ketika minum SINGULAIR (lihat "**Efek tidak diinginkan apakah yang dimiliki oleh SINGULAIR?**"), beritahukan kepada dokter anda.

Kapankah SINGULAIR tidak boleh diminum?

Jangan minum SINGULAIR bila anda:

- alergi terhadap salah satu komponennya.

Apakah yang harus saya beritahukan kepada dokter saya (atau penyedia layanan kesehatan) sebelum menggunakan SINGULAIR?

Beritahukan kepada dokter anda (atau penyedia layanan kesehatan) mengenai masalah medis atau alergi apapun yang anda miliki.

Penggunaan pada perempuan hamil

Perempuan yang hamil atau merencanakan kehamilan sebaiknya konsultasi kepada dokter mereka sebelum minum SINGULAIR.

Penggunaan pada ibu menyusui

Tidak diketahui apakah SINGULAIR keluar di air susu ibu. Anda sebaiknya berkonsultasi dengan dokter anda sebelum anda minum SINGULAIR bila anda sedang menyusui atau merencanakan menyusui.

Dapatkah saya minum SINGULAIR bersama dengan obat lainnya?

Secara umum, SINGULAIR tidak terganggu dengan obat lainnya yang anda minum. Akan tetapi, beberapa obat dapat mempengaruhi kerja SINGULAIR, atau SINGULAIR mempengaruhi kerja obat lainnya. Penting untuk memberitahukan kepada dokter anda mengenai semua obat yang anda gunakan atau akan digunakan termasuk obat tanpa resep.

Dapatkah saya mengendarai atau mengoperasikan mesin ketikan minum SINGULAIR?

SINGULAIR tidak mempengaruhi kemampuan anda mengendarai atau mengoperasikan mesin.

Bagaimana cara minum SINGULAIR?

Minum SINGULAIR satu kali sehari dengan atau tanpa makanan, sesuai resep dokter.

- Dosis untuk orang dewasa dan remaja usia 15 tahun keatas untuk mengobati asma adalah satu tablet 10-mg sehari.

Untuk pasien dengan asma, minum SINGULAIR satu kali sehari pada malam hari.

Jika Anda sudah minum SINGULAIR satu kali sehari, jangan mengambil dosis tambahan untuk asma akibat olahraga.

Untuk pasien dengan asma terinduksi olah raga yang belum minum SINGULAIR, minum SINGULAIR 2 jam sebelum berolah raga.

- Dosis untuk dewasa dan remaja usia 15 keatas adalah satu tablet 10-mg,

Selalu bawa obat inhalasi anda untuk berjaga terhadap serangan asma. Jangan minum SINGULAIR dengan dosis tambahan dalam 24 jam dari dosis sebelumnya.

Penting untuk melanjutkan minum SINGULAIR selama dokter anda meresepkan agar dapat mengontrol asma anda. SINGULAIR dapat mengobati asma anda hanya bila anda minum obat ini secara berkesinambungan.

Apa yang harus saya lakukan bila terjadi overdosis?

Hubungi dokter anda segera.

Tidak dilaporkan terjadi efek samping pada sebagian besar laporan overdosis. Gejala yang paling sering dilaporkan pada keadaan overdosis adalah nyeri perut, mengantuk, haus, sakit kepala, muntah dan hiperaktivitas.

Apa yang harus saya lakukan bila saya terlupakan satu dosis?

Usahakan minum SINGULAIR sesuai resep. Akan tetapi, bila anda terlupakan satu dosis, lanjutkan jadwal seperti biasa yaitu satu tablet atau satu paket sekali sehari.

Apakah efek tidak diiginkan yang dimiliki oleh SINGULAIR?

Obat apapun dapat memiliki efek tidak diinginkan, yang disebut efek samping. SINGULAIR secara umum dapat ditoleransi baik. Pada beberapa penelitian, efek samping yang sering terjadi adalah nyeri perut, sakit kepala, haus, diare, hiperaktivitas, asma, kulit bersisik dan gatal, serta ruam. Berbagai efek samping ini biasanya ringan dan terjadi sama banyak pada pasien yang minum SINGULAIR atau plasebo (pil yang tidak mengandung obat).

Disamping itu, hal berikut ini dilaporkan:

- infeksi saluran napas atas
- meningkatkan kemungkinan perdarahan, jumlah trombosit darah rendah
- reaksi alergik [termasuk bengkak pada wajah, bibir, lidah, dan/atau tenggorok (yang dapat menyebabkan kesulitan bernapas atau menelan), bentol, ruam, dan gatal]
- perubahan perilaku dan mood [agitasi seperti perilaku agresif atau permusuhan, depresi, disorientasi, gangguan memusatkan perhatian, bermimpi tidak normal, merasa cemas, halusinasi, insomnia, iritabilitas, gangguan ingatan, gejala obsesif kompulsif, tidak dapat

tidur, tidur berjalan, bicara gagap, berpikir dan melakukan untuk bunuh diri, gemetar, pergerakan otot yang tidak dapat dikontrol]

- pusing, mengantuk, kebas, kejang yang sangat jarang terjadi
- palpitasi
- perdarahan hidung; inflamasi paru
- diare, dispepsia, mual, muntah
- hepatitis
- memar, reaksi kulit berat (eritema multiformis) yang dapat terjadi tanpa tanda awal
- nyeri sendi, nyeri otot dan kram otot
- mengompol pada anak-anak
- lemah/lelah
- bengkak
- demam

Beritahukan kepada dokter atau ahli farmasi anda bila anda mengalami gejala yang tidak biasa, atau bila mengalami gejala yang berkelanjutan atau memberat.

Bagaimana saya dapat belajar lebih banyak mengenai SINGULAIR dan kondisi apa yang dapat diresepkan?

Anda dapat memperoleh informasi lebih lanjut dari dokter atau ahli farmasi anda, yang memiliki informasi lebih detail mengenai SINGULAIR dan kondisi anda.

Berapa lama saya dapat menyimpan obat saya ?

Jangan gunakan obat ini setelah tanggal kadaluarsa yang dituliskan dengan delapan angka setelah tulisan Exp. Date pada kotak dan blister. Dua angka pertama menunjukkan tanggal; dua angka kedua menunjukkan bulan; dan empat angka terakhir menunjukkan tahun.

Bagaimana cara menyimpan SINGULAIR?

Simpan pada suhu ruangan di tempat yang kering.

Jauhkan semua obat dari jangkauan anak-anak.

Apabila ada keluhan efek samping, silakan hubungi PT Organon Pharma Indonesia Tbk, Jakarta. Telepon : (021) 31107001; Email : dpoc.indonesia@organon.com

HARUS DENGAN RESEP DOKTER

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