CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-830/S008

MEDICAL REVIEW(S)

Hilfiker
JAN 24 2000

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20-830	APPLICATION TYPE:	Supplement SE1-008
SPONSOR:	Merck Research Labs (MRL)	PROPRIETARY NAME:	Singulair ®
CATEGORY OF DRUG:	LTD4 leukotriene antagonist	USAN / Established Name:	Montelukast Sodium
		ROUTE:	oral
MEDICAL REVIEWER:	Lydia I. Gilbert-McClain, M.D.	REVIEW DATE:	1/24/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
6/24/99	6/25/99	Efficacy supplement	
9/10/99		Safety update report	Electronic submission

RELATED APPLICATIONS (if applicable)

Document Date:	Application type:	Comments:
December 21,1996	NDA 20-829	Montelukast adult indication
February 21, 1997	NDA 20-830	Montelukast pediatric indication 6-14- year olds

Overview of Application/Review:
This is an efficacy supplement to NDA 20-830 Montelukast Sodium (Singulair ®) for the indication of the 4-mg chewable tablet in 2- to 4- year old children with asthma. The safety profile of the 4-mg tablet in this age group is similar to the safety profile in the 6- to 14- year old age group and this dose is expected to be efficacious based on the pharmacokinetic data. The supplement is approvable from a clinical standpoint.

Outstanding Issues:
None

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Recommended Regulatory Action:

New Clinical Studies: _____ Clinical Hold _Study May Proceed

NDAs:

Efficacy / Label Supp.: XXX Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: Jan 24 2000

Medical Team Leader: /S/ Date: 1/24/00

CC: ORIG NDA 20-830/S-008
HFD-570/DIV FILE
HFD-570/MEYER
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RESUME

Montelukast (Singulair ®) developed by Merck Research Labs (MRL) is approved for the treatment of asthma in adults and in children 6 years of age and above. With this efficacy supplement, Merck is seeking approval for the use of the drug in 2- to 5- year old asthmatics. Since the chewable tablet is approved down to age 6, there were two main questions to be answered to support approval in 2- to 5- year olds: (1) The selection of the right dose predicted to be effective, answered by the pharmcokinetic study and (2) The safety and tolerability of that dose answered by the clinical safety study. Therefore, this sNDA consists of data from a pharmacokinetic study and a chronic asthma study designed to look primarily at the safety and tolerability of the drug in this age group. The chronic asthma study has a one-year extension period, which is ongoing. Both of these studies are multicenter and multinational. Additional safety data is provided from a 4-month safety update report that provides information about the serious adverse events from the chronic asthma study and from post-marketing experience from off- label use. Below is a summary of the safety data derived from these studies and the safety update report.

EXECUTIVE SUMMARY OF SAFETY

Montelukast 4 mg- chewable tablet (CT) administered to 2- to 5- year old asthmatics once a day has a similar safety profile to 6-to 14-year old asthmatics who receive the 5- mg tablet once a day. The data provided confirm that the montelukast 4-mg CT appears to be sufficiently safe in 2- to 5-year old children when given once a day.

Review of the safety data from the pharmacokinetic [PK] study (protocol 066) and from the chronic asthma study (protocol 072) showed that most of the adverse events that occurred with montelukast 4 mg CT in 2- to 5-year olds, were similar to adverse events that occurred in 6- to 14-year olds taking montelukast 5 mg once daily.

Of the 15 patients in the PK study who received montelukast 4 mg CT as a single dose, only 3 of them had an adverse event. None of these adverse events were serious or drug related.

The interim analysis of safety from the chronic asthma study provided data on 192 patients who received monteluakst for ≥ 6 weeks. The only significant difference in adverse events between montelukast and placebo was in the respiratory system with a significantly lower incidence in the montelukast arm (60.8%) Vs 76.5% in the placebo arm (p=0.007).

The experience from the chronic asthma study suggests that the 2-to 5-year olds were capable of chewing the tablet without any problems. There were no

instances of choking in the children receiving montelukast but one child in the placebo arm had one episode of choking while eating a pretzel.

Similar to the experience in 6- to 14- year old asthmatics, no clinically significant laboratory abnormalities occurred in the chronic asthma study. There were only 4 laboratory adverse events that were felt by the investigator to be drug-related but none were serious nor did any of these events cause study dropouts. Concerns that leukotriene-inhibitors could cause adverse effects on ALT/AST levels were not substantiated.

There were 6 dropouts for drug-related adverse events, three of which were associated with drug overdose. Although the drug over dose was considered serious, the adverse experiences as a result of the overdose were not. However, the patients were discontinued because of unblinding.

A safety update report (SUR) submitted subsequent to the sNDA, provided safety data from 619 patients completing 12 weeks of therapy with montelukast 4-mg (chronic asthma study period II) once a day. Data were also provided from 516 patients in the extension period (period III) of the chronic asthma study as well as post-marketing safety experience reported to WAES. These reports indicated that the safety profile of montelukast 4-mg in 2- to 5- year olds continued to have a safety profile consistent with the safety profile seen in older pediatric patients aged 6- to 14-years.
One MedWatch report received subsequent to the SUR cited a case of elevated alkaline phosphatase in a 43-month-old female child from France who entered the extension period of the chronic asthma study. There were no reported liver function tests abnormalities. The alkaline phosphatase was of bone origin and returned to normal approximately 10 weeks later. Although the reporting physician considered this adverse event serious and drug-related, this is the only case report of this laboratory adverse event and may represent an idiosyncratic reaction. To date, there have been no other reports of elevated alkaline phosphatase in association with the use of montelukast in adults or children.

In conclusion montelukast 4-mg CT once daily appears to be sufficiently safe for use in 2- to 5- year-old asthmatic children.

APPROVABILITY

Based on the acceptable safety profile, as reviewed in this document, and an acceptable PK linkage, as reviewed by Dr. Chen, montelukast 4-mg CT is approvable from a clinical standpoint for use in 2- to 5- year old asthmatics.

1.0 INTRODUCTION

Montelukast is a selective LTD4 leukotriene antagonist developed by MRL and marketed under the trade name Singulair ®. It is currently approved for the treatment of asthma in adults and children 6 of age and above. The approved dose is one 10-mg film coated tablet (beige) once daily in adults and adolescents age 15 years and above, and one 5-mg pink cherry-flavored chewable tablet, once daily in 6- to 14- year old children. Patients take the tablet at bedtime without regard to meals.

Montelukast has been well tolerated in clinical studies. Results of pooled data from adult phase 1 through phase 3 studies demonstrated that 2606 patients were exposed to montelukast. In pediatric studies, 321 children 6- to 14 years of age were exposed to montelukast and the drug was generally well tolerated [vol. 20.2:262-263]

1.1 Reviewer Approach and Notations

Chemical structure, pre-clinical data, and clinical pharmacokinetics of the drug are not reviewed here. Dr. Chen, of the Office of Clinical Pharmacology and Biopharmaceutics (DPEII), has reviewed the PK model used to determine the dose in the 2- to 5- year old age group. Consequently, the medical officer review focused on the safety profile coming from the PK study, the chronic asthma study, and the safety update report. Additional safety information from a MedWatch report and from the AERS datamart in consultation with the Division of Risk Evaluation I were also reviewed.

1.2 Explanation of Terms and symbols

References in brackets [ ] refer to volume and page number from the application hard copy [Volume: page number].

In the two studies in the patient demographics section the term 'Mestizo' is used by the sponsor and in this review to describe a race. This is a term used in Latin America to define someone of mixed parentage (Latin American and American Indian).

WAES = Worldwide Adverse Experience system
QOL = Quality of life
Bold italic = Reviewer's comment

2.0 ADMINISTRATIVE HISTORY

NDA 20-829 for use of montelukast in adult and adolescent asthmatics aged 15 years and older and NDA 20-830 for use of montelukast in asthmatics aged 6- to 14 years were approved in February 1998.

Prior to submitting this sNDA to NDA 20-830, a meeting with Merck and the Agency was convened on November 7, 1997 to discuss the proposed sNDA. The Division agreed that a complete study report (CSR) from a pharmcokinetic study (protocol 066) and safety and tolerability data from an interim analysis from an ongoing chronic asthma study (protocol 072) would be adequate to support the proposed supplemental application. At that meeting, the Division also agreed that efficacy data would not be necessary for approval of the proposed supplement, based on the 1994 Pediatric Rule.

In a follow up telephone conversation with the Division on December 7, 1998 the Division asked Merck to submit a 4-month safety update report (SUR) from the chronic asthma study with serious adverse events and any post-marketing data obtained from currently marketed formulations. Merck also agreed to the Division's request to revise the "PRECAUTIONS, Pediatric use" subsection of the package insert with the proposed supplemental application.

3.0 DOSE SELECTION FOR THE PEDIATRIC POPULATION AGE 2 – 5 YEARS

The pediatric dose for the chewable tablet was selected to provide a pharmacokinetic (AUC) profile comparable to that of the 10-mg film-coated tablet (FCT) in adults. One pharmacokinetic study was conducted (protocol 066) in 15 patients aged 2 to 5 years. Since only a limited amount of blood could be obtained from these patients, Merck used a population pharmacokinetic approach to estimate the AUC. The AUC_{pop} in 2- to 5- year olds was calculated using a non-linear mixed effect one-compartment model fitted to the plasma concentration data. The PK model was validated using prior adult and pediatric plasma concentration data. The estimates of AUC_{pop} and the standard errors were similar to the mean AUC's and standard errors computed using conventional methodology.

4.0 Protocol no. 066: An open, 1-period, single-dose, multicenter study to evaluate the safety, tolerability, and AUC_{pop} (AUC determined by a non-linear mixed –effect model) of montelukast sodium (montelukast) administered as a chewable formulation in 2- to 5-year old children with asthma

4.1 SUMMARY

This single dose, multicenter, pharmacokinetic study establishes the pharmacokinetics of montelukast 4-mg chewable tablet (CT) in 2- to 5- year old children with asthma. The sponsor, Merck Research Labs, used a population pharmacokinetic approach to estimate the pharmacokinetic parameters. Using a non-linear mixed effect-one-compartment model fitted to the plasma concentration data, the sponsor established that the AUC_{pop} after a single dose of montelukast 4-mg CT, was comparable to the AUC_{pop} after a single dose of the 10-mg film coated tablet (FCT) in adults. The T_{max} was shorter and the C_{max} was larger for the 4-mg CT in the 2-to 5-year olds compared with that of the historical 10-mg FCT adult group. These differences in T_{max} and C_{max} were not unexpected and were comparable to what was previously seen in the 6- to 12-year old age group (protocol 036 and 039). The shorter T_{max} should not affect efficacy since the mean trough for the 4-mg CT in the pediatric group is greater than the trough value of the 2-mg FCT in adults, which demonstrated clinical effects throughout the dosing interval (historical data). Montelukast 4-mg CT given as a single dose is safe and well tolerated in 2- to 5- year old patients.

4.2 STUDY DESCRIPTION

DESIGN: Multicenter, one-period, single dose open label study with montelukast 4-mg CT in fifteen 2- to 5- year old asthmatics.

POPULATION: Fifteen 2- to 5-year old asthmatic children from three clinical centers: US, Peru, and Chile.

OBJECTIVE: To determine the AUC_{pop} and the safety and tolerability of montelukast 4- mg CT in 2-to 5-year old asthmatics.

CRITERIA: To be included in the study, patients had to be in otherwise good health without any clinically significant disease other than asthma, weigh 10 to 20 kg, be able to chew a tablet and have parental/legal guardian consent. A physician must have diagnosed asthma and patients had to have at least three episodes of asthma within the year prior to the prestudy visit. Patients were

excluded if any illness in the opinion of the investigator could confound the results of the study or pose additional risk to the patient.

CONDUCT: Patients who fulfilled the inclusion and exclusion criteria had a prestudy visit 4 to 7 days prior to the treatment day. At the prestudy visit, the investigator did a complete physical examination, vital signs, temperature, height, and weight (in kilograms) and drew blood for chemistry, hematology studies, and the pretreatment montelukast drug assay. In preparation for the treatment day, patients did not receive oral β-agonists for 24 hours prior to dosing. Patients fasted from 12 midnight prior to the dosing day except for water and apple juice, which they were allowed to have up to one hour before dosing. Thirty minutes before dosing, the investigator did vital signs and inserted a heparin lock into a forearm vein for drawing blood. The patients chewed the montelukast 4-mg CT, and drank 50 ml of water under observation. Patients ate a snack of cereal, milk, and clear apple juice 2 hours after dosing. Patients ate lunch at least 4 hours after dosing, and dinner 8 hours after dosing. Patients were discharged after 12 hours and returned 1 hour prior to the 24-hour postdose time point. Each patient was randomly assigned to one of two sampling schedules according to a computer-generated randomization. In this manner, a population pharmacokinetic approach was used to estimate the pharmacokinetic parameters of interest (specifically AUC_{tlop}). The sponsor used two distinct plasma sampling schedules with four sampling times in each schedule to increase the number of time points available for analysis as shown in Table 1.

Table 1. Sampling times for blood collection for pharmacokinetic parameters

	No. of patients	Sampling times (hours)						
		0	1.5	2	4	8	12	24
Schedule A	8	x	x		x		x	
Schedule B	7	x		x		X		x

All patients returned for follow up 48 to 72 hours post dose. The study procedures at the prestudy visit, treatment day, 24-postdose period, and poststudy visit are outlined in Table 2.

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Table 2. Schedule of Study Procedures (Clinical observations and Laboratory Measurements)

Procedure	Prestudy visit	Predose	Treatment Day (Visit 1) Hours Post dose 1.5	2	4	8	12	24 Hours Postdose (Visit 2)	Poststudy visit or Discontinuation (Visit D)
Informed consent	x								
Selection criteria	x								
Vital signs	x	x		x	x	x	x	x	x
Tympanic membrane temp.	x	x						x	x
Height and weight	x								
Physical exam	x								x
Heparin lock/catheter insertion	x	x							
Laboratory safety (blood)	x								x
Montelukast - schedule A	x		x		x		x		
Montelukast schedule B		x		x		x		x	

4.3 PATIENT DISPOSITION

Fifteen patients received one 4-mg montelukast CT. Approximately half of them were 5 years of age. The demographic characteristics of the patients at the three study sites are depicted in Table 3

TABLE 3. Demographic Characteristics of the Patients

	Male (M)	Female(F)	Race	Age years/n	Total
Clinica Ricardo Palma, Lima Peru	4	3	Mestizo/6 Caucasian/1	5-year olds/3 4-year olds/1 3-year olds/1 2-year olds/2	7
Children's Mercy Hospital, Kansas City, MO	0	4	Black/3 Caucasian/1	5-year olds/2 2-year olds/2	4
Hospital San Borja-Arriaran, Santiago, Chile	3	1	Caucasian/4	5-year olds/2 4-year olds/1 2-year olds/1	4
Age range 2 to 5. Height range (cm) 84.0 to 118.0 Weight range (Kg) 12.0 to 21.5					

4.4 PARAMETERS

The primary PK parameter was the AUC_{pop} of montelukast in 2-to 5- year old patients with asthma. The one- compartment model selected was validated with prior adult and pediatric plasma concentration data from protocols 034 and 039. (These two protocols were PK studies in 9- to 14, and 6- to 8-year old patients

with asthma respectively). Using prior adult and pediatric data, the sponsor prospectively selected sampling schedules that provided an estimate of AUC_{pop} within one standard deviation of the mean AUC obtained in the conventional manner. The T_{max}, C_{max}, and $t_{½}$ were also measured.

4.5 RESULTS

Pharmcokinetics

The AUC_{pop} after a single 4-mg CT dose of montelukast in 2- to 5-year old children was comparable to the AUC_{pop} after a single 10-mg FCT dose in the adults (2721 and 2595 ng/hr/mL respectively). The estimate of T_{max} was shorter and of C_{max} was larger for the 4-mg CT pediatric group compared with that of the historical 10-mg FCT in the adult group. Although the $t_{½}$ estimate for the 4-mg CT pediatric group was slightly shorter than the estimate for the 10-mg FCT historical adult control group, the $t_{½}$ estimate was within the range of that seen in adults. The mean trough value for the 4-mg CT pediatric group was greater than the trough value of the 2-mg FCT in adults. Since the 2-mg FCT dose in adults demonstrated clinical effects throughout the dosing interval the shorter $t_{½}$ estimated in the pediatric group is not expected to affect efficacy. The following graph shows the plasma concentrations for montelukast 4-mg CT and 10-mg FCT.

Observed (Mean) and Population Plasma (Predicted) Concentration Profiles for the 4-mg CT Pediatric (Protocol 066) and the 10-mg FCT Adult Groups (Protocol 034)

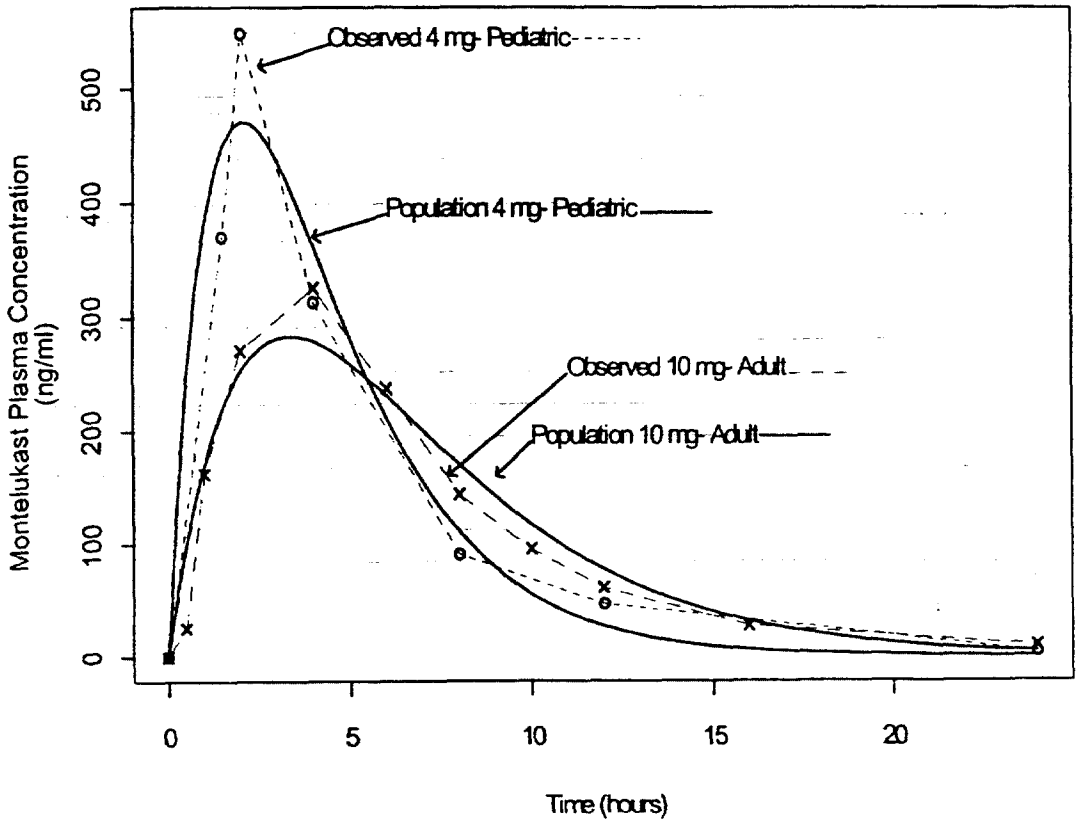


Table 4 shows the comparison between pharmacokinetic parameters of the 4-mg CT and the 10-mg FCT.

Table 4

	AUC_{pop}	C_{max}	T_{max}	$t_{½}$
4 mg CT	2721 ± 164.39	471.01± 65.27	2.07±0.30	3.17±0.20
10 mg FCT (historical data)	2595 ± 164.53	283.71± 54.35	3.36 ±0.60	4.09±0.09

4.6 SAFETY REVIEW (CLINICAL)

There were three clinical adverse experiences in 3 of the 15 patients. There were no dropouts, deaths, or serious adverse events. Two patients had diarrhea and one patient had an upper respiratory tract infection. These patients had no clinically significant changes in physical examination or vital signs at the follow up visit 48 to 72 hours after dosing. The investigator did not consider the adverse events to be drug-related. Table 5 summarizes the 3 adverse events.

Table 5. Summary of Clinical adverse events

Adverse Experience	Gender/ Age	Study Day (Relative to Dose)	Duration	Outcome	Comments
Infection. Upper respiratory	M/3	5 days	3 days	Recovered	Mild decreases in bicarbonate, glucose and creatinine and mildly elevated eosinophils. Repeat labs normal.
Diarrhea	M/5	2 days	2 days	Recovered	
Diarrhea	F/5	1 day	5 minutes	Recovered	Mildly elevated AST 4 days post dose but AST was mildly elevated prior to dosing.

4.7 SAFETY REVIEW (LABORATORY)

There were no clinically significant abnormal laboratory results. One patient with an increased serum creatinine, decreased glucose, decreased serum bicarbonate and slightly elevated eosinophils (0.603THS/μ/l, normal 0.57 THS/μ/l) 4 days after the treatment, also had a respiratory tract infection. These tests were normal upon repeat testing 7 days later. Four of the 15 patients had elevated AST but these elevations were not clinically significant and all patients had mildly elevated AST prior to receiving montelukast. Table 6 summarizes the abnormal AST results [ULN 34 U/L].

Table 6: AST results [ULN = 34U/L]

Gender/age	Pre-dose value	Post-dose value	Comment
F/5	37 (4 days)	49 (4 days), 36 (12 days)	Diarrhea. One episode
F/2	38 (4 days)	38 (4 days)	
M/2	53 (4 days)	24 (1 day), 43 (4 days)	
M/4	49 (4 days)	24 (1 day), 37 (4 days)	

4.8 REVIEWER'S COMMENTS

This study demonstrates that montelukast 4-mg CT given in a single dose is safe and tolerable in 2- to 5-year old asthmatics. The AUC_{pop} after a single 4-mg CT dose of montelukast in 2 to 5-year old children is comparable to the AUC_{pop} after a single 10-mg FCT dose in adults (historical data) The estimated shorter half life for the 4-mg CT should not affect efficacy because trough levels are higher than that of the lowest effective (2-mg) adult dose.

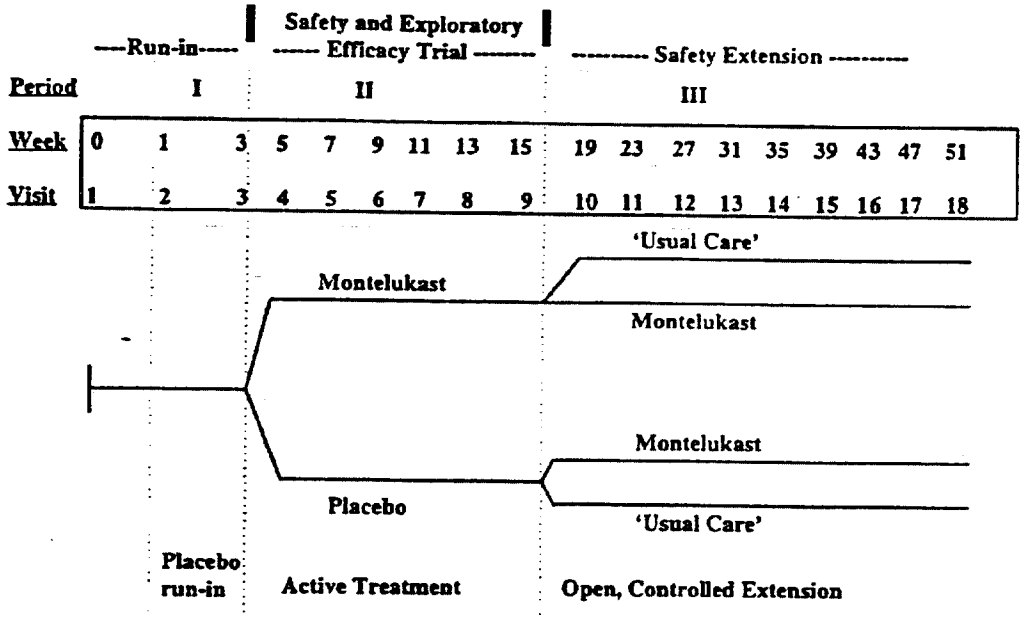
5.0 (Protocol 072): A Multicenter, Double-Blind, Randomized, Parallel-Group Chronic Asthma Study Comparing Montelukast with Placebo in 2- to 5-Year-Old Patients

5.1 Summary

This multicenter chronic asthma study compares the adverse event profile of montelukast 4 mg CT with placebo in 2- to 5- year old asthmatics. The interim analysis results of the 12-week double-blind period indicates that montelukast 4 mg CT administered once daily at bedtime was generally safe and well tolerated. The safety profile of montelukast was derived from the treatment experience of 212 patients completing ≥ 6 weeks of therapy. There were fewer adverse events of the respiratory system in the montelukast group than in the placebo group and overall the incidence of adverse experiences in the other body systems was generally similar between treatment groups. Adverse experiences of skin and skin appendages had higher frequencies in the montelukast group but venomous bites/stings, urticaria, and pruritus accounted for most of them. Six patients (2.8%) who received montelukast had clinical adverse events deemed to be drug-related by the investigator. There were no deaths reported in the interim analysis. A safety update report submitted subsequent to the supplemental new drug application showed a similar safety profile for montelukast 4-mg CT in 2- to 5-year old asthmatics.

5.2 STUDY DESCRIPTION

DESIGN: A 12-week, multicenter, double blind, parallel-group study with an open-label extension period for 36 weeks. The study design is depicted in the figure below.



The study had three periods. Patients and parents/guardians were not aware of the three distinct study periods.
Period I: A single blind, 2-week, placebo run-in period.
Period II: A double blind 12-week period where patients were randomized to montelukast 4 mg CT, or placebo.
Period III: An open controlled extension period for 36 weeks where patients received montelukast or "usual care." Patients in the "usual care" group were treated with inhaled/nebulized cromolyn or inhaled/nebulized corticosteroids. Patients who were already using inhaled or nebulized corticosteroids or inhaled/nebulized cromolyn when they entered the study did not change their dose if they were allocated to the "usual care" group. Patients did not change their diet during the study.

POPULATION: 314 asthmatic patients ages 2- to 5-years old from 58 study centers (40 US and 18 international centers in 15 countries) participated in period II.

OBJECTIVES: (1) To determine the adverse experience profile of montelukast compared with placebo over the 12-week double-blind period; (2) to determine the safety and tolerability of the administration of montelukast for up to 1 year in 2- to 5-year old patients with asthma; (3) to determine the effect of montelukast, compared with placebo on exploratory efficacy endpoints; (4) to evaluate the effect of montelukast, compared with placebo, on total blood eosinophil counts.

CRITERIA: To be included in the study, patients must have had a history of asthma diagnosed by a physician at least within the past year, parents/guardians must have consented to the patient's participation, patients must have been in otherwise good health, and must have been able to chew a tablet. Patients were excluded form the study if among other things they had any active, acute or chronic pulmonary disease other than asthma, any major surgical procedure in the prior four weeks, sinus disease in the last 3 weeks, a history of intubation for asthma, or asthma exacerbation in the prior month requiring hospitalization.

CONDUCT: After a one-week screening period with eligibility assessment, patients entered a 2-week baseline placebo run- in period (period I). During the eligibility assessment, patients had a complete physical examination including a gross neurological examination, height, and weight measurements. Sitting blood pressure, respiratory rate, temperature, and pulse were measured every two weeks in periods I and II and every 4 weeks in period III. The investigator gave patients capable of performing the peak flow maneuver an ——— peak flow meter. Patients received the peak flow meter any time during the study, whenever the investigator felt that the patient was able to perform the maneuver. The investigator established the patient's "personal best" and instructed the parent/guardian in the proper use and handling of the instrument. Patients were issued practice dairy cards in period I and they were reviewed at follow up visits in period I to ensure that data were entered correctly. At the third visit in period I, instructions for the completion of the self-administered Caregiver Asthma-Specific Quality of Life Questionnaire (a diary of questions of daytime and nighttime asthma symptoms) were reviewed with the parents/guardians. Patients qualified for randomization if they met a prespecified diary score, were compliant with the test drug (placebo), and their parents/guardians demonstrated an adequate understanding of the diary questions. Patients were not randomized if they required oral, intravenous, intramuscular or newly instituted inhaled corticosteroid therapy, theophylline therapy, subcutaneous or long-acting β-agonists, inhaled or nebulized cromolyn or required hospitalization or emergency room treatment for asthma. Up to 20% of patients were allowed to continue on inhaled/nebulized cromolyn and up to 30% on inhaled corticosteroids if they had been using a constant daily dose beginning at least 1 month before the prestudy visit. Qualified patients were randomly assigned to montelukast or placebo and continued to use "as-needed" β-agonist prescribed according to the investigator's usual clinical practice. Throughout this period patients had biweekly follow up visits. At these visits a number of follow up

procedures were done, including review of the asthma-specific QOL questionnaire and concomitant therapy, tablet counts, vital signs, laboratory tests (every 4 weeks), review of peak flow data, and review of the action plan for worsening asthma.

DATA ANALYSIS: An interim safety analysis was planned when at least 150 patients completed 6 weeks of the double-blind treatment (Period II). This analysis statistically was considered a screening exercise since it only looked at safety parameters. No α-level adjustment was planned in the final analysis. No efficacy data was analyzed. The primary objective of the interim analysis was to determine the adverse experience profile of montelukast compared with placebo over at least 6 weeks of double-blind therapy in a minimum of 150 patients. There were no a priori safety concerns identified in previous montelukast studies and therefore, there was no early stopping based on the interim analysis. Although the study was not designed for specific hypothesis testing, the sponsor used the Fisher's exact test to compare the frequencies of overall adverse events and adverse events by body system between treatment groups. Adverse events were listed and summarized by frequency of occurrence.

5.3. SAFETY MEASUREMENTS

Clinical evaluations: Physical examinations were done prior to randomization and at the completion of period II or at dropout.

Vital signs: Biweekly.

Laboratory safety tests
Done once during the placebo run-in period, every 4 weeks in period II, and every 3 months in period III. The following safety tests were done:
Hematology: hemoglobin, hematocrit, WBC (total and differential), platelets.
Blood chemistry: BUN, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate.

Peak flow monitoring: In patients capable of performing peak flow maneuvers, daily in the morning and evening.

Adverse experience monitoring
Monitored throughout the study and defined as any unfavorable and unintended change in structure, function, or chemistry of the body temporally associated with the use of the sponsor's product, whether or not considered related to the use of the product. Any worsening of a preexisting condition that was temporally associated with the use of the sponsor's product was also an adverse experience. Changes resulting from normal growth and development that did not vary significantly in frequency or severity from unexpected levels were not considered adverse events. Examples of this included typical crying in infants

and children, and teething. Adverse experiences were evaluated as mild, moderate or severe in terms of the intensity, and serious according to the definition of serious adverse events in 21CFR 314.80.

5.4. RESULTS

The interim safety analysis included all patients randomized by July 10, 1998, with ≥ 6 weeks of blinded data in house by October 5, 1998, for the US centers and by October 19, 1998, for the multinational centers. Patients randomized by July 10, 1998, who discontinued for any reason, were included in the analysis if their data were received by the data cutoff dates. The primary therapy period for the interim analysis extended from December 29, 1997, through September 28, 1998.

Participating centers: Fifty-eight study centers (40 United States) and 18 multinational in 15 countries contributed data to the interim analysis.

Patient accounting: A total of 314 patients entered in period II. The safety profile of montelukast was derived from the treatment experience of 212 patients with 199 of these completing ≥ 6 weeks and 139 of these completing 12 weeks of therapy. Table 7 shows the distribution of patients in the two treatment arms.

Table 7 Distribution of patients in the 2 treatment arms in Period II

	Montelukast 4 mg	Placebo	Total
ENTERED	212	102	314
Completed period II	139 (65.6%)	71 (69.6%)	210 (66.9%)
Discontinued	22 (10.4%)	11 (10.8%)	33 (10.5%)
Continuing in period II	51 (24.1%)	20 (19.6%)	71 (22.6%)

Patient characteristics: The characteristics of the 2- to 5- year old patients in the interim analysis are summarized in Table 8. Age is summarized in Table 8A.

Table 8: Characteristics of patients in the interim analysis

	Montelukast	Placebo
Male	130	57
Female	82	45
Caucasian	110	56
Black	28	13
Hispanic	51	21
Other races	23	12
Weight (kg) [Mean ±SD]	17.82 ±4.00	17.90 ±4.63
Height (cm) [Mean ±SD]	102.9 ±9.85	103.33 ± 8.47
Duration of asthma (yrs)	2.59 ±1.31	2.59 ±1.26

The patient's age in the clinical database is based upon age at randomization. Four patients turned 6 between visit 1 and visit 3, and one patient who was 6

years old at the prestudy visit was randomized because the patient's care giver did not know the child's correct date of birth. The age distribution of the children in the two arms (montelukast and placebo) is shown below.

Table 8A: Summary of age (years)

Age (years)	Montelukast	Placebo
2	45 (21.2%)	16 (15.7%)
3	51 (24.1%)	26 (25.5%)
4	62 (29.2%)	35 (34.3%)
5	50 (23.6%)	24 (23.5%)
6	4 (1.9%)	1 (1%)

Most of the patients (90.1%) had at least one secondary diagnosis and took at least one concomitant therapy post randomization. Concomitant therapies were similar in treatment groups and included antihistamines, antibiotics, acetaminophen, and beclomethasone diproprionate.

Reporting of Laboratory tests: Laboratory test results were reported based on a definition of predefined limits of change from baseline. Patients were classified as "above or below limit" if their change from baseline response fell outside of the predefined limits of change at least once during period II. Table 9 outlines the definition of predefined limits of change from baseline for the laboratory tests.

Table 9

Laboratory parameter	Definition
Hematocrit (%)	Decrease ≥ 20% from baseline and < LLN Increase ≥ 20% from baseline and > ULN
Platelet count ($10^3/\mu l$)	Decrease ≥ 25% from baseline and < LLN Increase ≥ 50% from baseline and > ULN
Total WBC ($10^3/\mu l$)	Decrease ≥ 20% from baseline and < LLN Increase ≥ 20% from baseline and > ULN
ALT (U/L)	Increase ≥ 100% from baseline and > ULN
AST (U/L)	Increase ≥ 100% from baseline and > ULN
Bilirubin (mg/dl)	Increase ≥ 50% from baseline and > ULN
ULN = Upper limit of normal LLN = Lower limit of normal U/L = International Units (IU)/L	

The sponsor did a more comprehensive analysis of ALT and AST by categorizing all patients with at least one postrandomization ALT and AST measurement into class intervals defined as multiples above the upper limits of normal from >1 to >4.

5.5 CLINICAL ADVERSE EVENTS

Two hundred and seventy (270) of the 314 randomized patients, (86.0%) had clinical adverse experiences. Table 10 summarizes the number of patients with clinical adverse events.

Table 10: Summary of clinical adverse events

Number (%) of Patients	Montelukast 4 mg chewable tablet (N=212)	Placebo (N=102)
	n (%)	n (%)
Evaluated	212	102
One or more adverse events	180 (84.9)	90 (88.2)
No adverse experience	32 (15.1)	12 (11.8)
Serious adverse events	6 (2.8)	5 (4.9)
Deaths	0	0
Discontinued due to adverse events	6 (2.8)	5 (4.9)
Discontinued due to serious adverse events	3 (1.4)	2 (2.0)

Adverse events were reported by body systems. Patients were counted more than once if adverse experiences occurred in multiple body systems but only once in a particular body system.
Twelve patients (11.8%) in the placebo arm and 32 patients (15.1%) in the montelukast arm had no adverse experiences.

5.5.1. Drug overdoses and associated adverse experiences

Five patients had overdoses after having been inadvertently allowed access to study medication by the caregiver. Three patients overdosed on montelukast in the range of 52 mg to 72 mg. There were no laboratory adverse experiences as a consequence. One patient, a 3-year-old female who ingested 52 mg of montelukast (14 tablets) developed mydriasis and thirst, which resolved within 24 hours. A 2-year-old male who ingested 64 mg of montelukast (16 tablets) complained of thirst, which resolved within 24 hours. A 3- year-old male ingested 72 mg (18 tablets) and was sleepy for one hour according to the caregiver. However, the patient returned to his baseline hyperactive state on arrival to the emergency room. These 3 patients were discontinued from the study because of their unblinding. Two patients "overdosed" on placebo without any associated adverse experiences. A patient who ingested 13 placebo tablets had study therapy interrupted for 2 days. The patient completed the double – blind section of the protocol but was not entered in the extension arm.

5.5.2. Serious Adverse Experiences other than Drug Overdoses

Six patients reported 7 serious adverse experiences other than drug overdose. These adverse experiences are depicted in Table 11 below. The investigators did not feel that these events were drug-related.

Table 11: Serious Adverse Events

Patient Age/Gender	Treatment	Adverse experience	Discontinued in Period II	Inclusion in extension arm
2y/o M Caucasian	Montelukast	Asthma worsening	Yes.	No
5 y/o M/Hispanic	Placebo	Asthma worsening Pulmonary infiltrate	Yes	No
4 y/o F/Black	Placebo	Asthma worsening	No	No
4 y/o M/Black	Placebo	Bipolar disorder	yes	No
4 y/o M Hispanic	Montelukast	Asthma	Yes (excluded medications received)	No
4 y/o F/Hispanic	Montelukast	Pneumonia	No	Yes

5.5.3. Non-Serious Adverse Experiences

The most frequently reported adverse experiences were fever, asthma, upper respiratory infections and pharyngitis. The only report of choking occurred in association with the ingestion of a pretzel in a patient in the placebo group. The incidence of asthma was 22.2% in the montelukast group and 34.3% in the placebo group representing a 12.1% difference with a 95% CI [0.86 to 24.77%]. Adverse events in the respiratory system totaled 129 (60.8%) in the montelukast group and 78 (76.5%) in the placebo group (p= 0.007). There were no other significant differences between treatment groups in the incidence of other clinical adverse experiences. For the body as a whole, there were 76 (35.8%) adverse events in the montelukast group and 41 (40.2%) in the placebo group with fever being the most common adverse event. In the cardiovascular system, there was one case of tachycardia and two cases of hematoma in the montelukast group but none in the placebo group. There were 56 (26.5%) adverse events in the digestive system in the montelukast group and 36 (35.3%) in the placebo group. Vomiting was the most common event in the digestive system occurring in 13.2% in the montelukast group and 19.6% in the placebo group. Adverse events were less than 5% in the hematologic and lymphatic system, the metabolic, nutritional and immune system, the musculoskeletal system, and the urogenital system. Headache (7.5% in the montelukast group and 8.8% in the placebo group) was the most common event among nervous system and psychiatric disorders. In the skin and skin appendages, 17.9% in the montelukast group and 10.8% in the placebo group reported adverse events. However, most of these were associated with venomous bites/stings, urticaria and pruritus. There were 5 episodes of urticaria in the montelukast group, which were not felt by the investigators to be drug-related. There were 17.9% adverse events in the special senses system in the montelukast group and 13.7% in the placebo group. Ear problems were more common in the montelukast group

(17.5%) than in the placebo group (8.8%). The following events occurred with a frequency ≥ 2% and more frequently in the montelukast group than in the placebo group: rhinorrhea (7.5%), thirst (2.4%), and leg pain (2.4%).

5.5.4. Drug-related Adverse Events

Six (2.8%) patients in the montelukast group and 4 (3.9%) patients in the placebo group had clinical adverse experiences determined by the investigator to be possibly drug related. The investigators did not feel that any of these events were definitely related to the drug. In the montelukast group, 3 of the adverse events were associated with drug overdoses. Only one patient in each treatment group discontinued treatment because of a "drug-related" adverse event. In the case of montelukast therapy, a 4-year old female patient developed paresthesia 2 weeks after being on montelukast. She complained of a sensation of ants walking on her hands and feet primarily at night. This patient's eosinophil count was 4.9% prior to starting montelukast (normal range 0 to 5 %) and was only slightly increased (6%) 4 days prior to the start of the parenthesis and at discontinuation of the study. A neurological work up was negative. The paresthesia completely resolved 5.5 months after discontinuing montelukast. One patient on placebo developed an itchy, raised photosensitive rash on all extremities one month after being on placebo. The rash and photosensitivity completely resolved one month after discontinuing the study.
Table 12 summarizes the AE's deemed to be drug-related.

Table 12: Summary of drug-related AEs

Montelukast (8 AE's in 7 patients)	Placebo (4 AE's)
Thirst* (4)	Rash (1)
Vomiting (1)	Photosensitive rash* (1)
Paresthesia** (1)	Irritability (1)
Abdominal pain (1)	Urticaria (1)
Mydriasis# (1)	
* = two cases associated with overdose. ** = Patient discontinued.	
# = Associated with overdose. The patient with mydriasis also had thirst.	

5.5.5. Discontinuations due to adverse events

Eleven of the 314 patients who received treatment discontinued because of adverse events. Twenty patients discontinued for other reasons. Table 13 summarizes the dropouts during the study.

Table 13: summary of Dropouts

# of Patients (%)	Montelukast	Placebo	Total
Entered	212	102	314
Discontinued (Dis.)	22	11	33
Dis. due to clinical AE	6	5	11
Withdrew consent	4	3	7
Protocol deviation	8	3	11
Lost to follow up	2	0	2
Other	2	0	2

5.6. Laboratory Safety

There were no significant differences between treatment groups in the laboratory events. Of the 314 patients who received treatment, there were 13 laboratory adverse events. Of these adverse events, 7 occurred in the montelukast group and 6 occurred in the placebo group. Of these adverse events, 4 were felt by the investigator to be drug-related (possibly, probably, or definitely).

There were no dropouts due to laboratory events. None of the laboratory adverse events were clinically significant. The investigators felt that four laboratory events (mild increase in AST, mild decrease in hemoglobin and WBC) were possibly related to montelukast. No patient had clinically significant elevated eosinophils.

No patient on montelukast therapy had elevated ALT but 4 patients had mild (> 1 and ≤ 1.25 ULN) elevation in AST which resolved without intervention. Three patients on placebo had elevations in AST and/or ALT > 2 ULN. One patient had mononucleosis with secondary non-icteric hepatitis, while the other two patients had hepatitis A. These three patients were discontinued from the study because of the infectious nature of their illness.

5.7 REVIEWER'S COMMENTS ON SAFETY

The results of the interim analysis suggest that montelukast 4 mg CT given once a day is well tolerated and safe in 2- to 5-year-old children with a safety profile similar to the safety profile seen in 6-to 14-year old patients taking montelukast 5 mg once daily (protocol 049). In this interim safety analysis, the incidence of adverse events in all body systems was generally similar for both treatment groups. However, more adverse events in the skin and appendages were seen in the montelukast group. Most of these events were due to venomous bites, stings, urticaria and pruritus. Choking was not a problem in this age group. The only episode of choking occurred in association with eating a pretzel in a patient on placebo. Adverse events were highest in the respiratory system in both groups but were significantly less in the montelukast group compared with the placebo group. Montelukast therapy did not cause clinically significant derangements in serum transaminases or eosinophil counts in these patients.

6.0. SAFETY UPDATE REPORT (SUR)

Subsequent to the submission of the supplemental new drug application (sNDA), Merck Research Laboratories (MRL) submitted a safety update report. This contains safety information up to June 30, 1999, for montelukast 4-mg chewable tablet.

6.1. Contents of the SUR

(1) Serious adverse events from protocol 072 (chronic asthma study) reported before June 30, 1999, and not included in the sNDA

(2) Postmarketing safety experience: Serious adverse events and montelukast overdoses received by the Merck Worldwide Adverse Experience System (WAES) data base from the following two sources:
(i) Serious adverse experiences reported during the chronic asthma study from sources other than case report forms (telephone call or facsimile prior to case report forms being received in-house)

(ii) Post-marketing safety experience reported to WAES from off-label postmarketing use in 2-to 5-year-old children.

6.2. Reporting periods

1. SUR-reporting period for clinical study data covered the time subsequent to the cutoff (08-Jan-1999) for inclusion of serious adverse experiences from clinical studies in the sNDA through 30-Jun-1999.
2. SUR-reporting period for post-marketing data covers the time subsequent to the cutoff (31-Dec-1998) for inclusion of serious adverse experiences from postmarketing use in the sNDA through 30-Jun-1999.

6.3 RESULTS

Six hundred and nineteen (619) patients completed the primary period of the chronic asthma study and 516 patients entered the safety extension. Twenty-two serious adverse experiences were reported in 17 children in the primary or extension periods of the chronic asthma study (protocol 072) as of 30-Jun-1999. There were no deaths. The most common serious adverse experiences were asthma and study drug overdose, each occurring in 4 children. No adverse experiences were associated with the episodes of study drug overdose.

6.3.1. Primary period (period II) chronic asthma study

Four (4) patients on blinded therapy had 4 serious adverse events (3 cases of asthma and 1case of gastroenteritis). The patient with gastroenteritis was previously reported in the sNDA as " fever." Table 14 summarizes these adverse events.

Table 14: Listing of patients with serious adverse events reported from 09-Jan-1999 through 30-Jun-1999 from sources other than case report forms chronic asthma study-primary period (period II). Patients are on blinded therapy.

Patient characteristic	Adverse experience	Drug relationship	Action taken	Outcome
F/3/Hispanic	Asthma	No	Discontinued	Recovered
M/4/Mestizo	Gastroenteritis**	No	Interrupted	Rec overed
F/3/Hispanic	Asthma	No	Discontinued	Still present
M/6/Hispanic	Asthma	No	Discontinued	Recovered
**This adverse event was reported as "fever" in the sNDA filed on 06-May 1999. Fever is no longer considered an adverse event by the investigator.				

6.3.2. Extension period (period III) chronic asthma study

Thirteen (13) children had 18 serious adverse experiences reported to WAES during the SUR-reporting period for clinical studies. Nine children in the montelukast group had 13 serious adverse events and 4 children in the "usual care" group had 5 serious adverse events. These are summarized in Table 15.

Table 15: Listing of patients with serious clinical adverse experiences reported from 09-Jan-1999 through 30-Jun-199 from sources other than case report forms-chronic asthma study- extension period (Period III)

Gender/age/Race	Total dosage	Adverse experience	Drug relationship	Action taken	Outcome
Montelukast 4 mg					
F/2/C	44 mg	Accidental ingestion by sibling	No		Recovered
	44 mg	Study drug overdose by sibling	No		Recovered
M/3/C	76 mg	Accidental ingestion by sibling	No		Recovered
	76 mg	Study drug overdose by sibling	No		Recovered
M/2/C	24 mg	Study drug overdose	Yes	Interrupted	Recovered
F/3/C	Not stated	Gastroenteritis	No		Recovered
	Not stated	Viral infection	No		Recovered
F/5/H	4 mg	Asthma			
F/4/M	4 mg	Atelectasis	No	Discontinued	Still present
M/4/C	4 mg	Abdominal pain	No	Discontinued	Recovered
M/4/C	4 mg	Bacterial infection	No	Discontinued	Recovered
F/3/C	4 mg	Seizure disorder	No		Recovered
M/4/C	28 mg	Study drug overdose	No		Recovered
"Usual care group"- cromolyn sodium, beclomethansone, budesonide					
F/2/C	3 puffs cromolyn	Bronchospasm	No	Interrupted	Recovered

M/4/B	300µg bechlomthasone	appendicitis		No	Recovered
M/3/Hispanic	250µg beclomethasone	Pneumonia	No	No	Recovered
M/5/C	300 µg beclomethasone	bronchospasm		No	Recovered
	300 µg beclomethansone	Sinusitis		No	Recovered
H= Hispanic, M=Mestizo B=black, C= Caucasian					

The patient who had seizures also had a history of febrile seizures and complained of headache, stomachache and had an elevated temperature of 104^0F . She was subsequently diagnosed with epilepsy. Therapy with montelukast was not interrupted. The physician felt that the epileptic febrile seizure was not related to therapy with montelukast.

6.3.3. Montelukast post-marketing experience in the 2-to 5-year old group

Preliminary review of prescription data as of 30-Apr-1999 indicates that the overall pediatric postmarketing treatment experience with montelukast is estimated to be greater than 140,000 patient-years. The proportion of off-label use by children under the age of 6 years included in the 140,000 patient-years of exposure is unknown. No reports of serious adverse experiences were received for pediatric patients aged 2-to 5-years during the SUR-reporting period for post-marketing data. Additionally, no follow-up information was received for serious adverse experiences reported in the 2-to 5-year-old age group presented in the supplemental application. There were three reports of overdose in the 2-to 5-year-old age group during the SUR-reporting period for postmarketing use however, no adverse experiences as a result of the montelukast overdose were reported.

7.0. REVIEWER'S COMMENTS ON THE SUR

The safety update report confirms that montelukast 4-mg CT appears to be sufficiently safe in 2-to 5-year old children and has a safety profile similar to 6-to 14-year old patients taking 5 mg once daily. All cases of overdose were associated with inadvertent access to the study medication when the medication was left unattended by the caregiver. No serious adverse events occurred in association with the overdoses.

8.0. MEDWATCH REPORTS

There has been one MedWatch report of a serious adverse event in one patient in the extension period of the chronic asthma study subsequent to the submission of the SUR.

A 43 month old female child from France who entered the extension arm of the study and had been on montelukast 4 mg developed elevated alkaline

phosphatase (AP) levels. Concomitant therapy included beclomethasone dipropionate and albuterol sulfate. The child complained of abdominal pain and tiredness, and had an increase in alkaline phosphatase[AP] (1444 IU/L, NR= 60-415) on 19-Jul-1999. The patient had been in the extension arm since 7-Jan-1999. Repeat AP levels were 4235 IU/L (NR =120-390), and 8541 IU/L (NR 100-270). Fractionation tests indicated that the AP was of bone origin and not liver (hepatic fraction 1% and bone fraction 99%). However x-rays did not show any bony abnormalities and bone mineral results were normal. At the time of the initial report, the AP was still elevated but was decreasing and the patient had recovered from the abdominal pain. The patient was discontinued from the extension. The reporting physician felt that the increase AP was serious and possibly related to montelukast. A follow up report indicated that the patient's alkaline phosphatase had returned to normal upon repeat testing on October 1, 1999, approximately 2 and a half months after the initial AP elevation was documented.

This is the first report of a clinically significant elevation in alkaline phosphatase levels occurring in association with montelukast therapy. No LFT abnormalities were reported and the AP fractionation indicated that the AP was of bone origin. There have been no reports of isolated elevations in alkaline phosphatase in adults or children receiving montelukast to date. This case may be due to an idiosyncratic reaction to the drug.

9.0 CONSULT FROM DIVISION OF RISK EVALUATION I

A consultation from the Division of Risk Evaluation I was requested to look at reports of seizures occurring in association with montelukast therapy. This request was not restricted to the 2- to 5- year old age group but included all patients exposed to montelukast up to March 1999. From ——— prescriptions for montelukast, there were 17 unduplicated cases of seizures, four of which did not appear to be related to montelukast therapy. The age of the patients ranged from 9- to 69-years of age. Six cases had documented recovery or positive dechallenge on discontinuation of montelukast. In the post-marketing reports submitted by Merck in the SUR, the only report of seizure in association with montelukast occurred in a patient with a known history of febrile seizures. ***Although seizure activity in association with montelukast was not a common occurrence and there were no spontaneous reports in the 2- to 5- year old age group, this adverse event should be reported in the "Post-Marketing" section of the label.***

10.0 CONCLUSIONS

Montelukast administered as 4-mg chewable tablet once daily to 2- to 5- year old asthmatics appears to be sufficiently safe and tolerable. No unexpected side effects occurred when the drug was given at this dose. The safety profile was similar to the safety profile of the 6- to 14-year old population receiving montelukast 5 mg once daily.

11.0 AUDITING

No sites were audited for this review.

LABELING REVIEW

The changes in the proposed label reflect the pharmacokinetic data and the safety profile for the 4-mg chewable tablet in 2- to 5- year old asthmatic patients.

Rhinorrea, thirst, and leg pain should be included in the pediatric section of the label as occurring ≥ 2 % more frequently in patients taking montelukast than in patients receiving placebo.

We recommend deleting the phrase [redacted] in the last sentence of the "Adverse Reactions" section so that it reads: [redacted]

[redacted]

Although it is an uncommon event seizures should be added as one of the reported adverse reactions to the "Post-Marketing Experience" section.

The overdose section of the label should include the clinical experience due to overdoses encountered in this study.