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# APPLICATION NUMBER

# 21-409

# Clinical Pharmacology and Biopharmaceutics Review

**Clinical Pharmacology and Biopharmaceutis Review**

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|---|---|
| **NDA:** | 21-409 |
| **Subject:** | Addendum to the original CPB review for NDA 21-409 |
| **Sponsor:** | Merck Pharmaceuticals |
| **Product:** | Singulair Oral Granules 4mg |
| **Drug:** | Montelukast Sodium |
| **Addendum date:** | Jul 26, 2002 |
| **Reviewer:** | Sandra Suarez-Sharp, Ph.D. |

In the original review for NDA-21-409 all the Cmax and AUC comparisons between different age groups (adolescents and pediatric patients section) were based on the geometric means rather that the arithmetic means of these pharmacokinetic parameters. These calculations have now been done based on arithmetic means and they are reflected in the labeling. It should also be noted that the correct range for Cmax in children 6 to 11 months of age is ———————ng/mL rather than ———————— ng/mL Therefore, this portion of the clinical pharmacology section should read as follows:

***Adolescents and Pediatric Patients:*** Pharmacokinetic studies evaluated the systemic exposure of the 4-mg oral granule formulation in pediatric patients 6 to 23 months of age, the 4-mg chewable tablets in pediatric patients 2 to 5 years of age, the 5-mg chewable tablets in pediatric patients 6 to 14 years of age, and the 10-mg film-coated tablets in young adults and adolescents 15 years of age.

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

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC (4296 ng*hr/mL [range 1200 to 7153]) was 60% higher and the mean Cmax (667 ng/mL [range 201 to 1058]) was 89% higher than those observed in adults (mean AUC 2689 ng*hr/mL [range 1521 to 4595]) and mean Cmax (353 ng/mL [range 180 to 548]). The systemic exposure in children 12 to 23 months of age was less variable, but was still higher than that observed in adults. The mean AUC (3574 ng*hr/mL [range 2229 to 5408]) was 33% higher and the mean Cmax (562 ng/mL [range 296 to 814]) was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6 to 23 months of age were similar to that of patients two years and above (see ADVERSE REACTIONS). The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

**RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-409 submitted on September 28, 2001. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB.

/S/

Reviewer
Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceuticals
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader /S/

cc

| | |
|---|---|
| NDA 21-409 : | Division File |
| HFD-870: | Malinowski, Hunt |
| HFD-570: | Fadiran, Starke, Chowdhury, Yu, Suarez-Sharp |

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
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Sandra Suarez
7/26/02 10:53:10 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
7/26/02 10:56:55 AM
BIOPHARMACEUTICS
I concur

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## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

| | |
|---|---|
| **NDA:** | 21-409 |
| **Proprietary Drug Name:** | Singulair [redacted] |
| **Generic Name:** | Montelukast Sodium |
| **Indication:** | Treatment of Asthma |
| **Dosage Form:** | [redacted] |
| **Strength:** | 4mg |
| **Route of Administration:** | Oral |
| **Dosage and administration:** | Children [redacted] to <6 years of age |
| **Applicant:** | Merck Research Laboratories |
| **Clinical Division:** | DPADP (HFD-570) |
| **Submission Date:** | September 28, 2001 |
| **Reviewer:** | Sandra Suarez-Sharp, Ph.D. |
| **Pharmacometric Consultant:** | He Sun, Ph.D. |
| **Team Leader:** | Emmanuel Fadiran, Ph. D. |

## 1. EXECUTIVE SUMMARY

Singulair™ (montelukast) is an antagonist of the Type I cysteinyl leukotriene (CysLT1) receptor that inhibits the effects of the pro-inflammatory cysteinyl leukotrienes. Singulair is currently indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 2 years of age and older. The original applications for Singulair 10 mg film-coated tablets (NDA 20-829), 5-mg chewable tablets (NDA 20-830) and a supplemental application for 4-mg chewable tablets (NDA 20-830/S-008) have been approved by the Agency.

In the present NDA (NDA 21-409) the sponsor, Merck Research Laboratories is seeking approval of Singulair ——— (Montelukast Sodium Oral Granules) as an alternate formulation to the 4 mg chewable tablet and as a primary formulation for pediatric asthma patients aged —— to <2 years. In support of this NDA the sponsor submitted the results of five clinical studies involving the montelukast ——— oral formulation. Three studies (P127, P183 and P090) presented pharmacokinetic data to support the use of the 4-mg oral granule formulation as an alternate to the 4-mg chewable tablet in patients aged 2 to 5 years. Two studies provided dosage, safety, and exploratory efficacy data (secondary endpoints) to support the use of the 4-mg oral granule formulation in patients aged 6 months to <2 years. One of these two studies (P136c/138) evaluated the systemic exposure of Singulair ——— 4mg in children 6 months to 2 years of age using a population pharmacokinetic approach.

Studies P127, P183 and P090 showed that the 4mg ——— formulation of montelukast was bioequivalent to the already approved 4mg chewable tablet and that the Cmax and AUC0-inf of the ——— formulation of montelukast were proportional to dose within the 2- to 6-mg dose range. In addition, these studies showed that applesauce did not affect the BA of montelukast delivered from the ——— formulation. Food did not affect the AUC of montelukast delivered from the ——— formulation, however food decreased Cmax by 35% and prolonged Tmax from 2.3 hrs to 6.4 hrs.

The population PK study showed that in children 6 months to < 1 year of age, AUC values ranged from 1200 ng*hr/mL to 7153 ng*hr/mL and the mean value was 48% higher than the observed in adults. Cmax ranged from 465.1 to 1057.8 ng/ml and the mean value increased by 79% compared to adults. The systemic exposure in the ≥ 1 year to <2 year olds was less variable, but still higher compared to that in adults. The mean AUC was 34% higher and the mean Cmax was 58% higher that those observed in adults (Table 1). No correlation was found between the pharmacokinetic parameters clearance and volume of distribution and weight or age.

**Table 1.** Mean montelukast population PK parameters following single administration of Singulair ——— 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets 4-mg to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM.

| | Montelukast formulations: ——— chewable tablets, film-coated tablets | | | | |
|---|---|---|---|---|---|
| PK Parameter | Children ≥6m to <1y | Children ≥1y to <2y | Children ≥6m to <2y | Children ≥2y to <6y | Adults |
| $AUC_{pop}$ (ng*hr/mL)[a] | 4298.2±542.1 | 4060.4±401.9 | 3907 ±286.4 | 2761.1±200.7* | 2644.8±154.1 |
| $Cmax_{pop}$ (ng/mL)[a] | 666.6±77.9 | 561.9±47.4 | 610.2 ±44.4 | 504.4±46.1* | 352.6±25.53** |
| $CL_{pop}$ (ml/min)[a] | 20.47±4.1 | 19.59±1.33 | 19.96±1.86 | 25.7±1.58* | 66.7±18.75 |
| Tmax (hr)[b] | 1.5±0.2 | 1.52±0.16 | 1.51±0.18 | 1.81±0.78 | 3.87±1.36** |
| T1/2[b] | 3.39±1.5 | 3.37±0.97 | 3.38±1.22 | 2.36±0.9 | 1.94±0.33[c] |

[a] mean ± SE; [b]mean±SD; *Data estimated using NONMEM from protocol no. 066; **calculated using non-compartmental methods; [c]based on 2CBM parameters

## 1.1 COMMENTS TO THE MEDICAL OFFICER

1. The submitted pharmacokinetic data support the use of the 4-mg oral granule formulation of

montelukast as an alternate to the 4-mg chewable tablet in patients aged 2 to 5 years.

2. Food did not affect the AUC of montelukast delivered from the ——— formulation, however food did decrease Cmax by 35% and change Tmax from 2.3 hrs to 6.4 hrs. The effect of food on the BA of Montelukast delivered from the film-coated tablet and chewable formulations has been studied in the past. While food did not affect Cmax and AUC for the film coated formulation, it did have similar effect as the one observed in the present case for the ——— formulation. Food decreased Cmax by 52% and decreased $F_{abs}$ from 73% (fasting) to 63% (fed) (data from NDA 20-830 submitted on 02/24/97). Although the effect of food on the Cmax of the chewable formulation was statistically significant, it was decided that this effect was not clinically relevant (clinical trial conducted without regards to meals or timing of food ingestion did not show any safety of efficacy concerns) and therefore, the findings were not reflected in the label.
3. There is no correlation between clearance (and therefore AUC), volume of distribution and weight or age in the group of children ≥6 months to < 2 years of age. This suggests that the dosage regimen in this group of children should not be based on weight.
4. High variability in exposure (AUC and Cmax) was observed in the children ——— to < 2 years of age, especially in the ≥6 months to < 1 years of age. A lower dose of Singulair ——— for this population would give a similar systemic exposure to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target AUC of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age receiving 4-mg of Singulair ———

**1.2 COMMENTS TO THE CHEMIST**

1. The sponsor has provided enough information to support the dissolution specification of Q=——— in 20 min.

**1.3 RECOMMENDATION**

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed NDA 21-409 submitted on September 28, 2001. The DNA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB. Please conveyed the labeling comments to the sponsor (see pages 22-23).

Reviewer
Sandra Suarez-Sharp, Ph.D. _____
Office of Clinical Pharmacology and Biopharmaceuticals
Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader _____

cc

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|---|---|
| NDA ———— : | Division File |
| HFD-870: | Malinowski, Hunt |
| HFD-570: | Fadiran, Starke, Chowdhury, Yu, Suarez-Sharp |

## 2. TABLE OF CONTENTS



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## 3. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Singulair™ (montelukast) is an antagonist of the Type I cysteinyl leukotriene (CysLT1) receptor that inhibits the effects of the pro-inflammatory cysteinyl leukotrienes. Singulair is currently indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 2 years of age and older.

In the present NDA (NDA 21-409) the sponsor, Merck Research Laboratories is seeking approval of Singulair ——— (Montelukast Sodium Oral Granules) as an alternate formulation to the 4 mg chewable tablet and as a primary formulation for pediatric asthma patients aged ——— to <2 years. The sponsor submitted the results of five clinical studies involving the montelukast ——— (oral) formulation. Three studies (P127, P183 and P090) presented pharmacokinetic data to support the use of the 4-mg oral granule formulation of montelukast as an alternate to the 4-mg chewable tablet in patients aged 2 to 5 years. Two studies provide dosage, safety, and exploratory efficacy data (secondary endpoints) to support the use of the 4-mg oral granule formulation in patients aged ———to <2 years. One of these two studies (P136c/138) evaluated the systemic exposure of Singulair ——— 4mg in children ——— to 2 years of age using a population pharmacokinetic approach. In accordance with the 1994 Pediatric Final Rule, the sponsor believes that the demonstrated efficacy of montelukast in adults and pediatric patients as young as 2 years of age in the treatment of asthma can be extrapolated to these younger patients.

Study P127 was as open label, randomized, 3-period, crossover study to determine the dose proportionality of the Montelukast ———formulation in healthy adults. This study showed that the Cmax and AUC0-inf of the ——— formulation of montelukast are proportional to dose within the 2- to 6-mg dose range.

Study P183 was a 3-period, single-dose, crossover study in healthy adult subjects to establish the bioequivalence of the 4-mg tablet and ——— formulations of Montelukast, and to evaluate the effect of food on the pharmacokinetics of the ——— formulation. This study showed that the Singulair ———formulation is equivalent to the Singulair chewable formulation as demonstrated by 90% CI applied to the geometric mean ratio for the AUC and Cmax pairs (Table 2).

**Table 1.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf comparing the ——— with and without a high fat meal and the ——— and the chewable tablet

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings | This reviewer's findings | Sponsor's findings | This reviewer's findings |
| MTL ———/MTL Chewable tablet | AUCinf | 0.95 | 0.985 | 0.91-0.99 | 0.936-1.035 |
| | Cmax | 0.92 | 0.92 | 0.84-1.01 | 0.837-1.01 |
| MTL ——— fasted/MTL ——— with high fat meal | AUCinf | 1.04 | 1.04 | 0.99-1.09 | 0.987-1.09 |
| | Cmax | 0.64 | 0.65 | 0.59-0.71 | 0.59-0.71 |

Food did not affect the AUC of montelukast delivered from the ——— formulation, however food did decrease Cmax by 35% and change Tmax from 2.3 hrs to 6.4 hrs (Table 1). This effect of food on the Cmax of the Singulair ——— formulation might be clinically irrelevant since the clinical trials have been conducted without regards

of food or time of administration with no indication for safety or efficacy concerns.

Study P090 was an open label, randomized, 3-period, crossover study to determine the bioequivalence of the chewable and ——— formulations of montelukast in healthy adult volunteers. This study showed that the Singulair ——— formulation was bioequivalent to the Singulair chewable formulation (4mg CW tablet) and that applesauce does not affect the bioavailability of montelukast delivered from the Singulair ——— formulation.

Study 136c/138 was an open label, single dose, multicenter study to evaluate the safety, tolerability, and plasma concentration profiles of Montelukast ——— in ≥ 6 months to 24 month old children. This study evaluated and compared montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax) obtained from the ≥6- to <24-month-old children after administration of a 4-mg dose of the ——— formulation of montelukast with historical data in adult subjects after administration of a 10-mg dose of the FCT of montelukast using a population PK approach. To have a more complete picture, this reviewer also analyzed the data generated in the 2 to 5 years olds receiving 4 mg chewable tablet using also a population PK approach.

This study showed that there is no correlation between Cmax (data not shown) or AUC and weight in the group of children ≥6 months to < 2 years of age receiving Singulair ——— 4mg (Figure 1). This suggests that the dosage regimen in this group of children should not be based on weight.

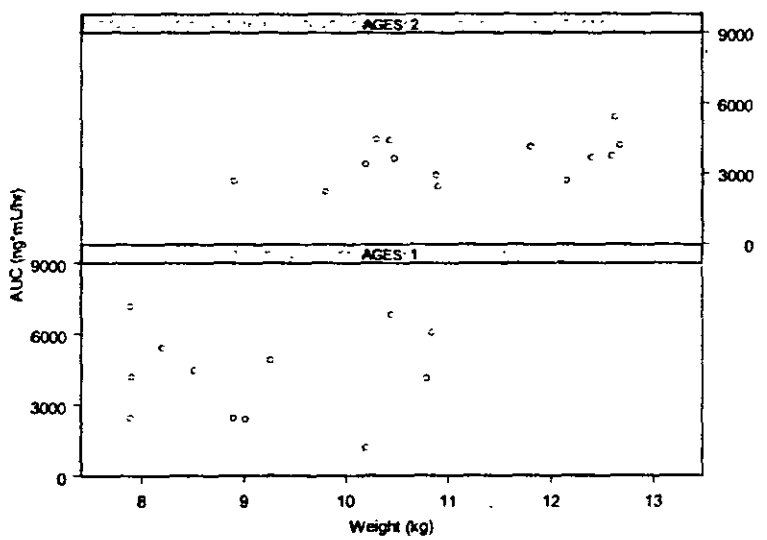



**Figure 1.** Individual AUC vs. WT in children receiving single dose of Montelukast ——— 4 mg. Ages 1 correspond to children ≥6 months < 1 year and ages 2 correspond to children ≥ 1 years to <2 years of age.

High variability in exposure (Cmax and AUC) was observed in children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age (Figures 2 and 3, respectively).

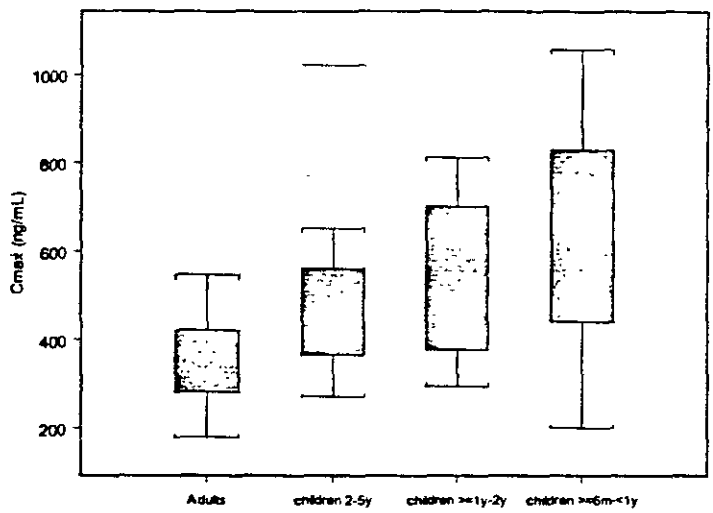



**Figure 2.** Box plot for population Cmax (Cmaxpop) following single administration of Singulair ——— : 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. Subjects 101 and 132 excluded from the 6m-2y old group.

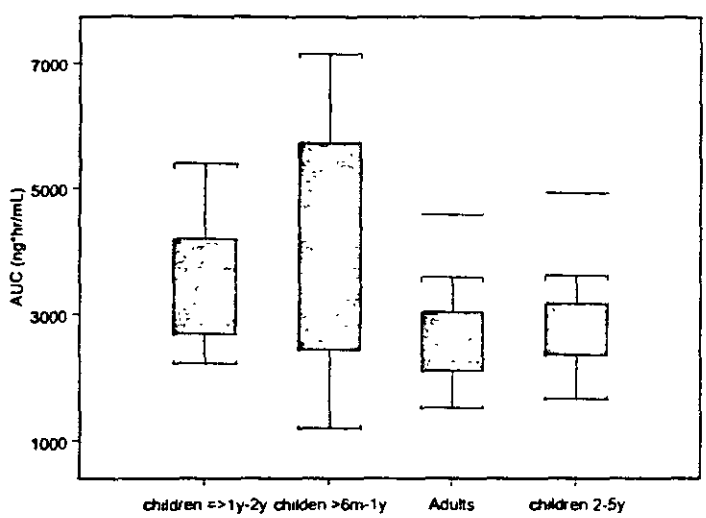



**Figure 3.** Box plot for population AUC (AUCpop) following single administration of Singulair ——— 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years, and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. The Cmax adult data was calculated using non-compartmental methods. Subjects 101 and 132 excluded from the 6m-2y old group.

Based on simulation studies, a lower dose of Singulair ——— to this population would give a similar average systemic exposure observed to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age.

## 4. QUESTION BASED REVIEW

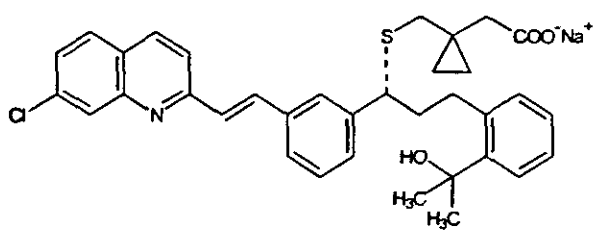
**Q1. What are the general attributes of Singulair 4mg ———**

**DL Chemical name:**

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

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

**Structural formula:**




**Molecular formula:** $C_{35}H_{35}ClNNaO_3S$

**Molecular weight:** 608.18

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

**FORMULATION**

Each packet of SINGULAIR 4-mg ———for oral administration contains 4.2 mg montelukast sodium, which is the molar equivalent to 4.0 mg of ———The ——— formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate (Table 1.1).

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**Table 1.1. Market Composition, Montelukast Sodium oral Granules, 4-mg and 4mg chewable tablets**

| Ingredient (mg) | 4-mg Chewable Tablet | 4-mg |
|---|---|---|
| Montelukast sodium | | |
| Mannitol, USP | | |
| Microcrystalline cellulose, NF | | |
| Hydroxypropyl cellulose, NF | | |
| Red Ferric Oxide, NF | | |
| Cherry flavor | | |
| Aspartame, NF | | |
| Magnesium stearate, NF | | |
| Total Weight | 240.0 mg | 500.0 mg |

**INDICATION (as per proposed label)**

SINGULAIR ——— is indicated for the prophylaxis and chronic treatment of asthma in pediatric patients ———

**DOSAGE AND ADMINISTRATION (as per proposed label)**

***Pediatric Patients 2 to 5 Years of Age***

The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet or one packet of SINGULAIR 4-mg ——— daily to be taken in the evening.

***Pediatric Patients ——— to 2 Years of Age***

The dosage for pediatric patients ——— to 2 years of age is one packet of SINGULAIR 4 mg ——— daily to be taken in the evening. Safety and effectiveness in pediatric patients younger than ——— of age have not been studied.

**Q2. What is known about the pharmacokinetics of Montelukast?**

The following pharmacokinetics of montelukast were presented in previous NDA (20-829).

***Absorption***

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

For the 5-mg chewable tablet, the mean $C_{max}$ is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean $C_{max}$ is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

***Distribution***

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11liters.

***Metabolism***

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

*In vitro* studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

***Elimination***

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile. In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

***Special Populations***

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

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

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

***Hepatic Insufficiency:*** Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast AUC following a single 10-mg dose. No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

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

***Adolescents and Pediatric Patients:*** The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents 15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients 15 years of age.

*Drug Interactions*

Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state did not cause clinically significant changes in the kinetics of theophylline, warfarin, digoxin, terfenadine oral contraceptive containing norethindrone 1 mg/ethinyl estradiol 35 mcg, prednisone or prednisolone.

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

**Q3. Was the to-be-marketed formulation used in the pharmacokinetic studies? Did the batches of Singulair ——— used in the PK studies meet dissolution specifications?**

The following formulations were used in the submitted PK studies. The batch sizes used in this study, as observed in Table 3.1 were ——— Formulation number MR-3808 was less than .. of the size of a full production batch (——— packets).

Table 3.1 Montelukast formulation used in this study

| PK study | Batch size (packets) | Site of manufacture | Control number | Formulation Number |
|---|---|---|---|---|
| P090 | ——— | Merck Frosst, CAN/PCI services | WP-E431 | MR-3808 |
| P127 | ——— | Merck Frosst, CAN/PCI services | CA-A630 | MR-3808 |
| P183 | ——— | ——— | CA-A870 | MR-4218 |
| P136c/138 | ——— | Merck Frosst, CAN/PCI services | CA-A678, CA-A704B, CA-A704, CA-A704D | MR-3808 |

According to the sponsor, the manufacturing process has remained essentially unchanged throughout development of this product with the exception of the manner of addition of the binder and drug solutions. In an early clinical batch (MR-3808) the binder and drug solutions were prepared ——— The NDA stability batches and commercial process still involve the ——— preparation of the binder and drug solutions; however, now the ———

The bioequivalence of these 2 formulations was tested in separate studies having the 4-mg chewable tablet as a reference. Those two studies showed that these two formulations of Singulair ——— are bioequivalent to the chewable tablet. Therefore, differences in batch size (lower than recommended) and manufacturing site and process changes may not affect the in vivo performance of these two formulations.

**Dissolution**

In the first submission to this NDA, the sponsor has originally proposed the following method and specifications:

Dissolution Parameters
Apparatus: No. 1 (baskets with 100 mesh)
Rotation Speed: 50 rpm
Dissolution Medium: [redacted]
Medium Volume: [redacted]
Medium Temperature: [redacted]
Sampling Volume: [redacted]
Sampling Time: [redacted]

**Specification**: Q= [redacted] in [redacted] minutes

In a latter submission received on May 3, 2002 the sponsor requested a change in specification to Q=[redacted] in 20 minutes. The reason for this change and its justification is as follows:

Recently, Merck conducted pharmaceutical process validation activities in order to demonstrate successful transfer of the manufacturing process to the full-scale equipment in the Merck Manufacturing Division facility in West Point, PA, and to demonstrate successful scale-up of the packaging operations at [redacted] According to the sponsor, with the exception of the dissolution results, all data generated against the validation protocol were within the prescribed acceptance criteria.

Dissolution results obtained for the three validation batches (Figure 3.1), using the test method described in the NDA, were outside the acceptance criteria in the protocol, and were different than those previously generated for key development batches, including the biobatch (MR-4218) (Figures 3.2 and 3.3). The results for the validation batches showed several low values at the 10 minute timepoint, and a limited number of low values at the 15 minute timepoint. All samples showed complete dissolution at 20 minutes for all validation and development batches (Figure 3.1).

Testing with single point sampling at 15 minutes provided statistically similar results for the validation batches compared to profile testing; however, a single non-conforming result ([redacted], which is outside the USP requirement of no values below Q - 25%) was obtained for the third validation batch during single point testing. For this reason, the sponsor is changing the specifications from Q=[redacted] in [redacted] to 20 min.

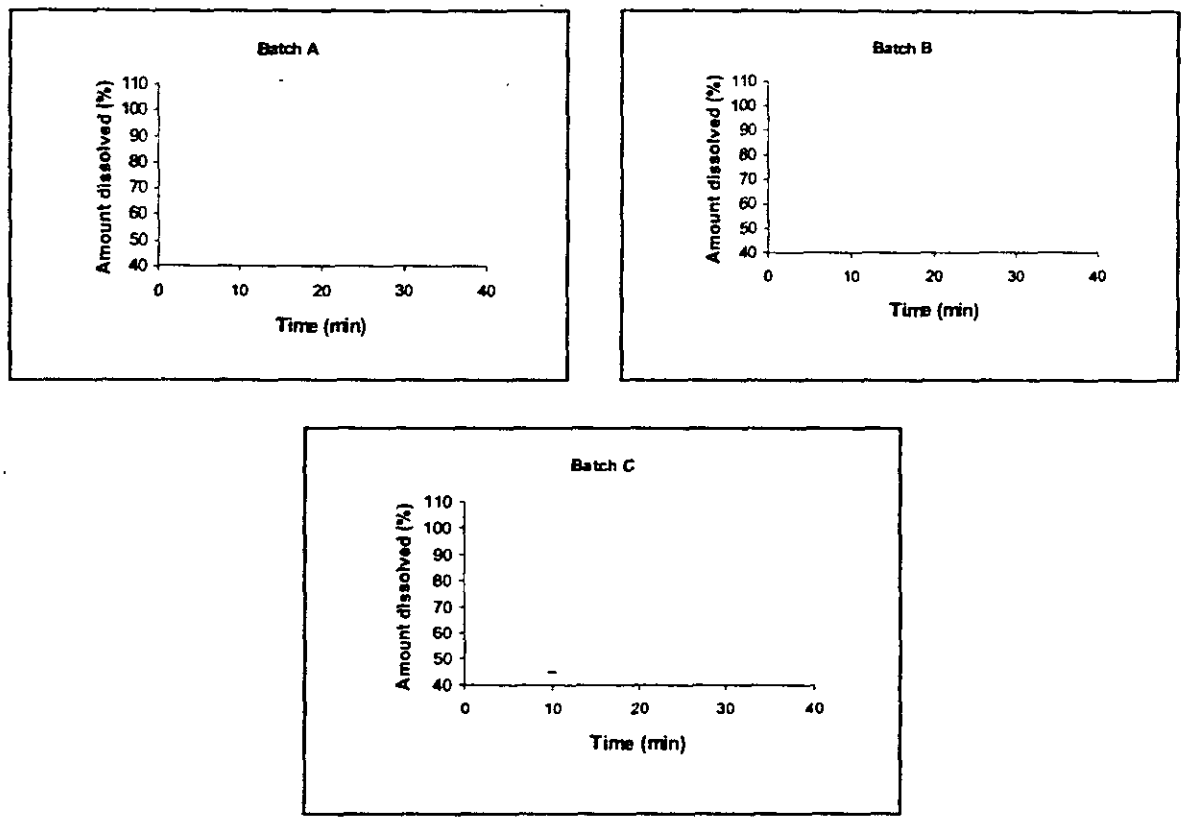


**Figure 3.1** Dissolution Profiles for Montelukast Sodium Oral Granules Validation Batches. Batch A= Batch 2089088; Batch B=Batch 2089090; Batch C=9249. N=40 samples per batch.

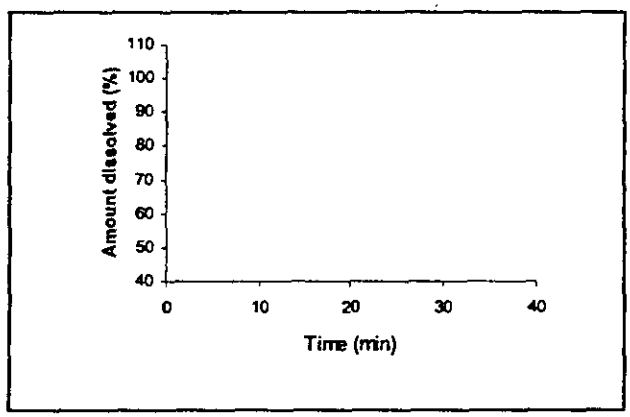


**Figure 3.2** Dissolution Profiles for Montelukast Sodium Oral Granules for biobatch MR-4212. N=40 samples.

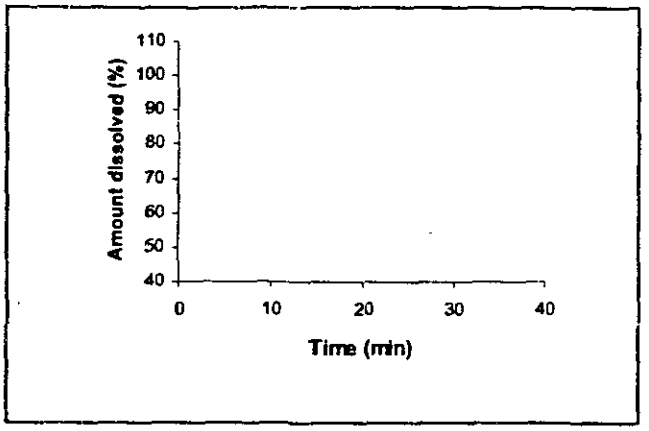


**Figure 3.3.** Dissolution Profiles for Montelukast Sodium Oral Granules for biobatch MR-3808. N=11 samples.

The dissolution data obtained during the validation process prompted detailed investigations of the manufacturing and packaging processes as well as the analytical testing practices. The result of these investigations show that the electrostatic charge of the product, together with the poor hydrodynamics within the dissolution apparatus, impact the data obtained using the current dissolution method.

A study in which the dissolution basket speed was changed by ——— showed more rapid dissolution at ——minutes for the validation batch 2089249 at the ——— speed, further suggesting that the hydrodynamics at the recommended ——— speed are not optimal for assessment of data against the current specification. However, according to the sponsor, since all historical data have been generated using the current method at ———, it was considered more appropriate to increase the duration of agitation from 15 to 20 minutes rather than to increase the basket speed. This reviewer agrees with this statement.

The sponsor considers that the lower dissolution data at the 10 and 15 minute timepoints are artifacts of the test method, and are not an indication of poor product quality. The sponsor believes that these results are not expected to have any adverse effect on the safety and efficacy of the product. This reviewer agrees with this statement since MR-3808 also showed low dissolution values at 10 min and this formulation was shown to be bioequivalent to the chewable tablet.

## CONCLUSION

- The sponsor has provided enough information to support the dissolution specification of Q=——, in 20 min.

**Q4. Are Cmax and AUC proportional with increments of dose following administration of Singulair ———**

YES.

Study P127 was conducted to assess dose proportionality after administration of 2-, 4-, and 6-mg single oral doses of the ——— formulation of montelukast. This was an open label, randomized, 3-period, crossover study conducted in sixteen subjects (10 men

[age range: 20-45 years] and 6 women [age range: 22-44 years]). This study showed that the Cmax and AUC0-inf of the ——— formulation of montelukast are proportional to dose within the 2- to 6-mg dose range as observed in Table 4.1 (90% confidence intervals).

**Table 4.1.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf comparing the ——— doses of 2, 4 and 6 mg

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings | This reviewer' findings | Sponsor's findings | This reviewer' findings |
| 2mg/4mg | Cmax | 103 | 103.3 | 88-121 | 88.4-120.7 |
| | AUCinf | 90 | 89.9 | 80-102 | 79.2-102.01 |
| 6mg/4mg | Cmax | 107 | 105.3 | 91-124 | 90.1-123.03 |
| | AUCinf | 96 | 94.9 | 84-108 | 83.6-107.7 |
| 2mg/6mg | Cmax | 97 | 98.1 | 83-113 | 83.9-114.6 |
| | AUCinf | 94 | 94.8 | 83-107 | 83.5-107.5 |

## CONCLUSION

- The Cmax and AUC0-inf of the ——— formulation of montelukast are proportional to dose within the 2- to 6-mg dose range.

**Q5. Was the ——— formulation of Singulair bioequivalent to the chewable formulation? Did high fat food affect the bioavailability of montelukast delivered from the ——— formulation? Did applesauce affect the BA of montelukast delivered from the ——— formulation?**

Two studies were conducted to assess for BE between the ——— formulation and the chewable tablet formulation. These two studies were conducted using different formulations of ———. As stated before in question 3, these formulations differ on batch size, manufacturing site and manufacturing process.

Study P183 was a 3-period, single-dose, crossover study in healthy adult subjects to establish the bioequivalence of the 4-mg tablet and ——— formulations of Montelukast. The formulation number used is this study was MR-4212.

This study also evaluated the effect of food on the pharmacokinetics of the ——— formulation. Thirty one subjects (20 men [age range: 19-43 years] and 11 women [age range: 21-44 years]) were included in this study and received the following treatment in a randomized fashion:

**Treatment A**: single 4-mg dose of the chewable tablet in the fasted state
**Treatment B**: single 4-mg dose of the ——— : formulation in the fasted state
**Treatment C**: single 4-mg dose of the ——— formulation after consumption of a high-fat breakfast.

This study showed that the Singulair ——— formulation is bioequivalent to the Singulair chewable formulation as demonstrated by 90% CI applied to the geometric mean ratio for the AUC and Cmax pairs (Table 5.1).

**Table 5.1.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf comparing the ——— with and without a high fat meal and the ——— and the chewable tablet

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings | This reviewer's findings | Sponsor's findings | This reviewer's findings |
| MTL ———/MTL Chewable tablet | AUCinf | 0.95 | 0.985 | 0.91-0.99 | 0.936-1.035 |
| | Cmax | 0.92 | 0.92 | 0.84-1.01 | 0.837-1.01 |
| MTL ——— fasted/MTL ——— with high fat meal | AUCinf | 1.04 | 1.04 | 0.99-1.09 | 0.987-1.09 |
| | Cmax | 0.64 | 0.65 | 0.59-0.71 | 0.59-0.71 |

This study also showed that food did not affect the AUC of montelukast delivered from the ———formulation, however food did decrease Cmax by 35% and change Tmax from 2.3 hrs to 6.4 hrs (Table 5.1).

The effect of food on the BA of Montelukast delivered from the film-coated tablet and chewable formulations has been studied in the past. While food did not effect Cmax and AUC for the film coated formulation, it did have similar effect as the one observed in the present case for the———formulation. Food decreased Cmax by 52% and decreased $F_{abs}$ from 73% (fasting) to 63% (fed) (data from NDA 20-830 submitted on 02/24/97). Although the effect of food on the Cmax of the chewable formulation was statistically significant, it was decided that this effect was not clinically relevant (clinical trial conducted without regards to meals or timing of food ingestion did not show any safety of efficacy concerns) and therefore, the effect of food on Cmax was reflected in the label.

Study P090 was an open label, randomized, 3-period, crossover study to determine the bioequivalence of the chewable and ——— formulations of montelukast in healthy adult volunteers. The formulation number used is this study was MR-3808.

This study also evaluated the effect of applesauce on the pharmacokinetics of the ——— formulation. Twenty-four subjects (9 men [age range: 24 to 43 years] and 15 women [age range:27 to 44 years]) were included in this study and received the following treatment in a randomized fashion:

- One pouch of 4-mg ——— (Treatment A)
- One pouch of 4-mg ——— to be delivered on 2 teaspoons of applesauce (Treatment B)
- One 4-mg CT (Treatment C)

This study showed that the Singulair ———formulation was bioequivalent to the Singulair chewable formulation (4mg CW tablet) (Table 5.2)

Table 5.2 Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf comparing the ——— with and without applesauce and the ——— and the chewable tablet

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings | This reviewer' findings | Sponsor's findings | This reviewer' findings |
| MTL ——— MTL Chewable tablet | AUCinf | 1.01 | 1.01 | 0.92-1.11 | 0.92-1.109 |
| | Cmax | 0.99 | 0.986 | 0.86-1.13 | 0.856-1.13 |
| MTL ——— fasted/MTL ——— with applesauce | AUCinf | 1.0 | 1.00 | 0.92-1.1 | 0.90-1.097 |
| | Cmax | 0.92 | 0.919 | 0.80-1.06 | 0.798-1.058 |

This study also demonstrated that applesauce did not affect the AUC of montelukast delivered from the ——— formulation (Table 5.2, Figure 5.2). It was also observed that applesauce increased Tmax from 2.1±1.1 to 3.4±1.2 hrs. This increase in Tmax might be clinically irrelevant since as stated before the clinical trials have been conducted without regards of meals and time of administration without concerns for safety and efficacy.

## CONCLUSIONS

- The Singulair ——— formulation is equivalent to the Singulair chewable formulation.
- Food did not affect the AUC of montelukast delivered from the ——— formulation, however food did decrease Cmax by 35% and change Tmax from 2.3 hrs to 6.4 hrs. This effect of food on the Cmax of the Singulair ——— formulation might be clinically irrelevant since the clinical trials have been conducted without regards of food or time of administration without indication for safety or efficacy concerns.
- Applesauce does not affect the bioavailability of montelukast delivered from the Singulair ——— formulation.

**Q6. Was the systemic exposure in children 6 months to 2 years of age following administration of Singulair ——— similar to the one in adults receiving Singulair 10mg film-coated tablets?**

**NO.**

Study P136c/138 was a population pharmacokinetic study conducted to assess the systemic exposure of a single dose of 4-mg Singulair ——— in children. This study was an open label, single dose, multicenter study to evaluate the safety, tolerability, and plasma concentration profiles of Montelukast ——— in ≥ 6 months to 24-month old children. This study compared montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax) obtained from the ≥6- to <24-month-old children after administration of a 4-mg dose of the ——— formulation of montelukast with historical data in adult subjects after administration of a 10-mg dose of the FCT of montelukast using a population PK approach. To have a more complete

picture, this reviewer also analyzed the data generated in the 2 to 5 years olds receiving 4 mg chewable tablet using also a population PK approach.

Subjects (32) received the following treatment in a randomized fashion:

- One pouch of 4-mg ——— to be delivered on 1 teaspoons of applesauce.

The sponsor used the SAS software to estimate the population PK of the drug. This reviewer used NONMEM software to reproduce the results submitted in this NDA Different models were fitted to the adult and children data separately and together.

When all the data was pool together, a 2-compartment model with first order absorption and elimination was used. The effect of covariates, such as weight and age were introduced into the basic adult and children model, and was evaluated based on the change in value of the objective function. Body weight was the only covariant that affected drug clearance (data not shown).

When data was handle separately, a 1-compartment model with first-order absorption and elimination best described the concentration-time data generated in children 6 month to 2 years of age. The analysis was done with the inclusion and exclusion of subjects 101 and 132 who appear to be outliers. The exclusion of these subjects did not affect the outcome of the average population PK parameters.

The sponsor used the SAS software to estimate the population PK of the drug. This reviewer used NONMEM software to reproduce the results submitted in this NDA. This reviewer fitted the adult and children data separately and together.

When all the data was pool together, a 2-compartment model with first order absorption and elimination was used. The effects of covariates, such as weight and age were introduced into the basic adult and children model (pooled data), and were evaluated based on the change in value of the objective function. Body weight was the only covariant that affected drug clearance (data not shown).

When data was handle separately, a 1-compartment model with first-order absorption and elimination was used to fit the concentration-time data generated in children 6 month to 2 years of age. The analysis was done with the inclusion and exclusion of subjects 101 and 132 who appear to be outliers. The exclusion of these subjects did not affect the outcome of the average population PK parameters.

A 2-compartment model with first order absorption and elimination better describe the adult data from protocol 034. The adult Cmax was calculated using non-compartmental methods and the children Cmax was calculated based on the estimates of ke, ka and Vd. T1/2 has calculated using the estimated rate of elimination.

The effect of covariates, such as weight and age were introduced into the basic adult and children models. The analysis showed no correlation between clearance (and therefore, AUC) and volume of distribution and weight or age in the group of children ≥6 months to < 2 years of age receiving Singulair ——— 4mg. This suggests that the dosage regimen in this group of children should not be based on weight.

This reviewer used WinNonlin in an attempt to estimate, which would be the most appropriate dose for this children population in terms of achieving similar exposure as that obtained in adults. Simulations were done using the estimated average PK parameters (post-hoc estimates) generated in the population PK analysis (data not shown).

High variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age (Table 6.1 and Figures 6.1 and 6.2, respectively). Based on simulation studies, a lower dose of Singulair ———: to this population would give similar systemic exposure observed to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target AUC of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age.

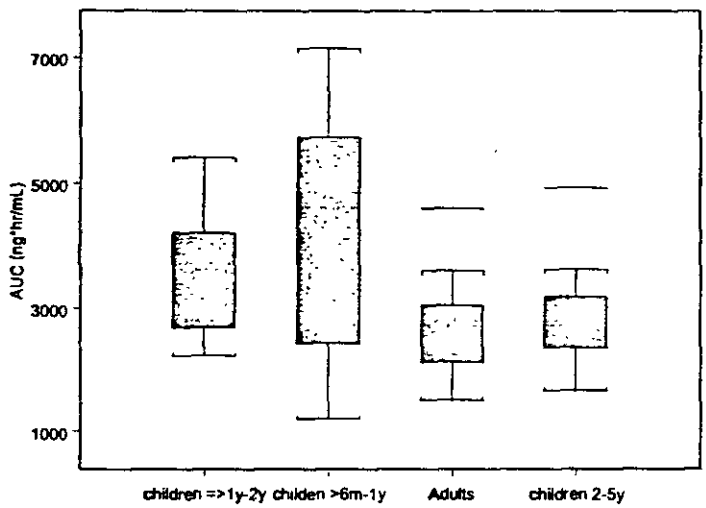


**Figure 6.1.** Box plot for population AUC (AUCpop) following single administration of Singulair ——— 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. Subjects 101 and 132 excluded from the 6m-2y old group.

**Table 6.1.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUC comparing different children populations to adults receiving montelukast

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings* | This reviewer' findings | Sponsor's findings** | This reviewer' findings |
| ≥6m to <1 y/adult | AUC | 135 | 148.1 | 102-154 | 119.3-183.9 |
| | Cmax | | 178.9 | | 141.4-226.4 |
| ≥1y to <2y/adult | AUC | 118 | 133.7 | 97-144 | 108.7-164.5 |
| | Cmax | | 157.8 | | 125.9-197.3 |
| ≥2y to <6 y/adult | AUC | 105 | 103.2 | 90-122 | 84.2-126.5 |
| | Cmax | | 141.8 | | 113.6-176.9 |

* CI back calculated from log-transformed scale; **sponsor reported 95% confidence intervals

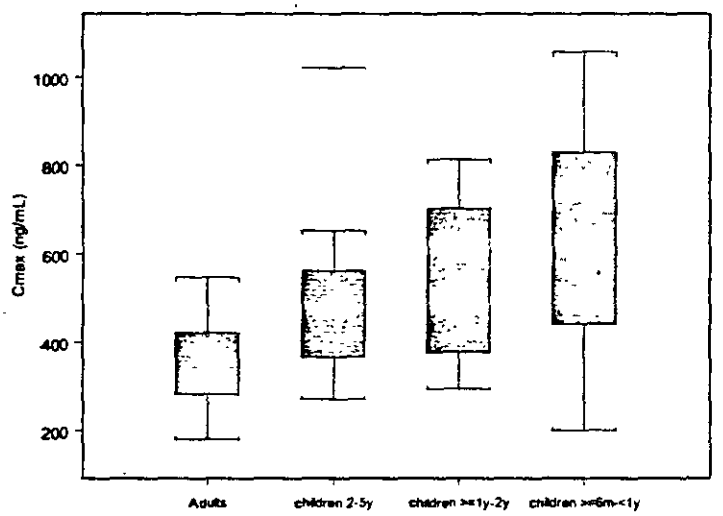


**Figure 6.2** Box plot for population Cmax (Cmaxpop) following single administration of Singulair ——— 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. The Cmax adult data was calculated using non-compartmental methods. Subjects 101 and 132 excluded from the 6m-2y old group.

## CONCLUSIONS

- There is no correlation between Cmax or AUC and weight in the group of children ≥6 months to < 2 years of age.
- High variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age. A lower dose of Singulair ——— to this population would give a similar systemic exposure to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age.

**Q7. Was the suitability of the analytical method supported by the submitted information?**

Yes, the sponsor submitted all the appropriate information that supports that the analytical methods used in ——— are accurate, precise, sensitive and specific. The lower limit of sensitivity was ——— Tables 7.1 to 7.4 summarized the performance of the method in each PK study.

**Table 7.1.** Assay performance (in-study validation) for Montelukast (Study P090)

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: |
| **Accuracy** | Satisfactory: |
| **Presicion** | Satisfactory |
| **Specificity** | Satisfactory |

**Table 7.2.** Assay performance (in-study validation) for montelukast (Study P127)

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: |
| **Accuracy** | Satisfactory |
| **Presicion** | Satisfactory: |
| **Specificity** | Satisfactory: |

**Table 7.3.** Assay performance (in-study validation) for montelukast (Study P183)

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: |
| **Accuracy** | Satisfactory: |
| **Presicion** | Satisfactory: |
| **Specificity** | Satisfactory: |

**Table 2.** Assay performance (in-study validation) for Montelukast (Study P136c/138)

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: |
| **Accuracy** | Satisfactory: |
| **Presicion** | Satisfactory: |
| **Specificity** | Satisfactory: |

APPEARS THIS WAY
ON ORIGINAL

16 pages redacted from this section of the approval package consisted of draft labeling

## 6.2 INDIVIDUAL REPORTS

**"An Open, Randomized, 3-Period, Crossover Study to Determine the Dose Proportionality of the Montelukast (MK–0476) ——— Formulation in Healthy Adults"**

Study Protocol 127
Study Completion Date (LPO): Oct 30, 1999
Investigator Name/Affiliation: ———
[ ]
Clinical Study Report Date Jul 19, 2001

### OBJECTIVE

- To evaluate the plasma concentration profile of 2-, 4-, and 6-mg single oral doses of the ——— formulation of montelukast.
- To assess dose proportionality after administration of 2-, 4-, and 6-mg single oral doses of the ——— formulation of montelukast.
- To evaluate the safety and tolerability of single oral 2-, 4-, and 6-mg doses of the ——— formulation of montelukast.

### SUBJECTS

Sixteen subjects (10 men [age range: 20-45 years] and 6 women [age range: 22-44 years]) met the inclusion criteria and were randomized. All subjects completed the study. Fifteen (15) subjects were Hispanic and one was black.

### STUDY DESIGN AND TREATMENT ADMINISTRATION

This was an open-label, randomized, 3-period, crossover study conducted in healthy adult volunteers. All fasted subjects each received 3 single-dose treatments of montelukast, administered in separate periods as determined by a computer-generated random allocation schedule. Each treatment was separated by a washout period of at least 96 hours. The test products were packaged individually for each subject for each treatment as follows:

**Treatment A**: One vial of 2-mg ———
**Treatment B**: One vial of 4-mg ———
**Treatment C**: One vial of 6-mg ———

### FORMULATION

The following formulations and batch numbers where used in this study.

**Table 1.** Montelukast formulations used in this study

| Test product | Potency | Formulation | Control number | Formulation Number |
|---|---|---|---|---|
| Montelukast | 2 mg | [ ] | CA-A630 | MR-4054 |
| Montelukast | 4 mg | | CA-A630 | MR-3808 |
| Montelukast | 6 mg | | CA-A630 | MR-4022 |

**Table 1a: Composition of Montelukast Sodium oral Granules, 2, 4 and 6 4 mg**

| | 2 mg | 4-mg | 6-mg |
|---|---|---|---|
| Ingredient (mg) | | Chewable Tablet | [redacted] |
| Formulation number | MR-4054 | MR-3808 | MR-4022 |
| Montelukast sodium | [redacted] | | |
| Mannitol, USP | | | |
| Magnesium stearate, NF | | | |
| Packaging | vial | pouch | vial |
| Total Weight | 500 mg | 500 mg | 500.0 mg |

## PHARMACOKINETIC MEASUREMENTS

### Blood sampling

Blood samples were taken at 0.0 hr (pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration of treatments and were for montelukast concentrations.

### Analytical Method

Plasma concentrations of montelukast were determined by HPLC assay procedure with fluorescence detection.

## DATA ANALYSIS

### Pharmacokinetic Analysis

The primary pharmacokinetic parameters used for the pairwise comparisons to evaluate dose proportionality were the dose-adjusted AUC0-inf and Cmax and were calculated using non-compartmental techniques. Other pharmacokinetic parameters, included the time of the maximum observed plasma concentration (Tmax) and the apparent elimination half-life (t½).

### Statistical Analysis

The pharmacokinetic parameters observed following single 2-, 4-, and 6-mg doses of the [redacted] formulation of montelukast were evaluated using an analysis of variance (ANOVA) model that contained factors for subject, period, and treatment. Carryover effect was assessed by adding such effect in the ANOVA model.

All pairwise GMRs for the dose-adjusted AUC and Cmax were determined with corresponding 90% CIs and were compared with the prespecified bounds (0.70, 1.43) sequentially. Before comparison of the 90% CI of the GMR of the 6-mg and 2-mg doses could be made to the bounds (0.70, 1.43), both 90% CIs for the comparisons of the 4-mg and 2-mg ratio and the 6-mg and 4-mg ratio had to be contained within the (0.70, 1.43) interval. According to the sponsor, for the [redacted] formulation to be considered dose proportional in the 2- to 6-mg range, all 3 CIs needed to be within the (0.70, 1.43) interval.

An additional analysis for assessing dose proportionality was made using the log dose-unadjusted AUC0-inf Cmax versus dose with a supportive regression line (i.e. log (AUC) = alpha + beta*log (dose). According to the sponsor, a slope coefficient consistent with the value of 1.0 would be indicative of dose proportionality over the dose range used in this study.

## SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, 12-lead ECGs, and vital sign evaluations.

## RESULTS

### Analytical Method Pre-Study Validation

**Recovery:** Not reported

**Limit of Quantitation:** Not reported in this submission

**Stability**: not reported in this submission

**Table 2.** Assay performance (in-study validation) for montelukast

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: |
| **Accuracy** | Satisfactory: |
| **Presicion** | Satisfactory: |
| **Specificity** | Satisfactory: |

### Pharmacokinetic Results

The mean plasma concentration-time profiles for montelukast in healthy adult subjects receiving a single dose of 2, 4 and mg oral dose of MTL formulations in the fasted state are shown in Figure 1. Table 1 summarizes the pharmacokinetics of montelukast for these three treatments. Individual values for the dose-normalized Cmax and AUC0-inf for the treatments are presented in Figures 2 and 3, respectively.

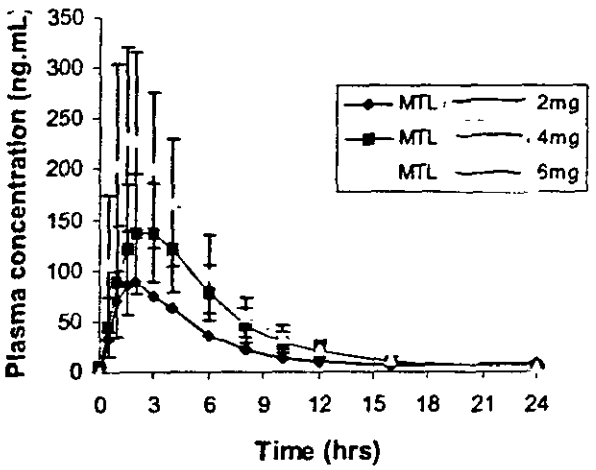


**Figure 1.** Mean Montelukast plasma concentration-time profiles following single administration of MTL 2, 4, and 6 mg MTL to healthy adult volunteers. Bars represent ±SD.

**Table 3.** Mean (±SD) montelukast pharmacokinetic parameters following single administration of MTL ——— 2, 4 and 6 mg-fasted to healthy adult volunteers.

| | Montelukast formulations | | |
|---|---|---|---|
| | 2 mg | 4 mg | 6 mg |
| **PK Parameter** | | | |
| $AUC_{0-\infty}$ (ng*hr/mL)[a] | 499 (133) | 1069 (220) | 1529 (312) |
| Cmax (ng/mL)[a] | 88 (25.3) | 164.2 (42.9) | 264.7 (72.6) |
| Tmax (hr)[a] | 1.8 (0.3) | 2.8 (1.3) | 1.8 (0.6) |
| T1/2[b] | 3.3 | 3.7 | 3.9 |

[a] Arithmetic mean; [b] harmonic mean

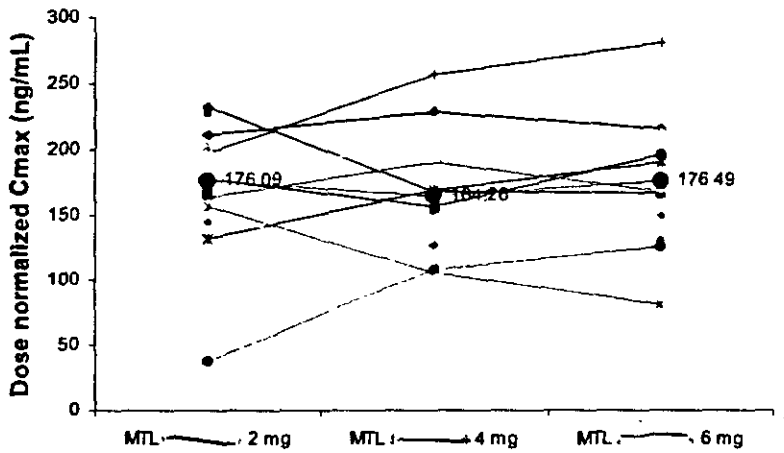


**Figure 2.** Individual Montelukast Cmax values following single administration of MTL ——— 2, 4 and 6 mg to healthy adult volunteers. Individual values were dose normalized to the 4 mg dose.

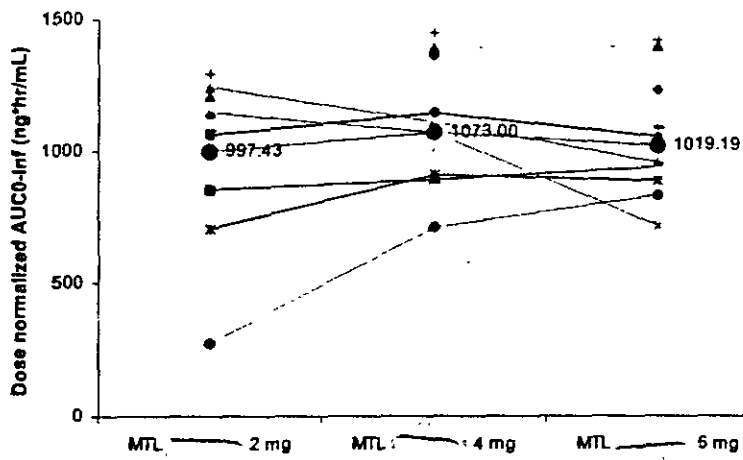


**Figure 3.** Individual Montelukast AUC0-inf values following single administration of MTL ——— 2, 4 and 6 mg to healthy adult volunteers. Individual values were dose normalized to the 4 mg dose.

**Table 4.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf comparing the doses of 2, 4 and 6 mg

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings | This reviewer' findings | Sponsor's findings | This reviewer' findings |
| 2mg/4mg | Cmax | 103 | 103.3 | 88-121 | 88.4-120.7 |
| | AUCinf | 90 | 89.9 | 80-102 | 79.2-102.01 |
| 6mg/4mg | Cmax | 107 | 105.3 | 91-124 | 90.1-123.03 |
| | AUCinf | 96 | 94.9 | 84-108 | 83.6-107.7 |
| 2mg/6mg | Cmax | 97 | 98.1 | 83-113 | 83.9-114.6 |
| | AUCinf | 94 | 94.8 | 83-107 | 83.5-107.5 |

## DISCUSSION

The results shown in table 4 indicate that the PK parameters, namely Cmax and AUC0-inf increase proportionally to the dose in the range of 2 to 6 mg in the adult population. A dose proportional increase has been show previously for the film-coated tablet of montelukast over the 1- to 50-mg dose range, with only a slight deviation from linearity noted at 50-mg dose. Thus, the results from the ——— formulation in this study were consistent with the dose proportionality previously described with another formulation of montelukast.

## CONCLUSION

The Cmax and AUC0-inf of the ——— formulation of montelukast are proportional to dose within the 2- to 6-mg dose range.

## DISSOLUTION

The dissolution of montelukast sodium oral granules, 4 mg is carried out in an ——— medium containing —— w/v of the : ———————————, using USP apparatus I (baskets with 100 mesh) at a speed of 50 rpm. The amount of montelukast sodium released at the prescribed timepoint(s) is determined by HPLC using conditions which rapidly and reliably quantitate the levels of active in the dissolution medium. The HPLC method has been validated for accuracy, injection and method precision, linearity, selectivity, solution stability and robustness.

Dissolution Parameters

Apparatus: No. 1 (baskets with 100 mesh)
Rotation Speed: 50 rpm
Dissolution Medium: ———————
Medium Volume: ———
Medium Temperature: ———
Sampling Volume: ———
Sampling Time: ———

**Specification**: Q=—— in 20 minutes

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The dissolution results for the batches considered in this study are as follows:

**Table 1d: Dissolution data for the 2, 4, and 6 mg formulation of Singulair**

| Time | 2mg | 4mg | 6mg |
|---|---|---|---|
| 10 min. Mean | 97% | 73% | 94% |
| Range | | | |
| RSD % | 0.1 | 25.7 | 0.9 |
| 15 min. Mean | 98% | 98% | 96% |
| Range | | | |
| RSD % | 5.6 | 7.7 | 0.9 |
| 20 min. Mean | 98% | 99% | 97% |
| Range | | | |
| RSD % | 5.6 | 6.6 | 1.2 |
| 30 min. Mean | 96% | 99% | 96% |
| Range | | | |
| RSD % | 5.5 | 6.5 | 1 |

## CONCLUSION

The batches tested meet dissolution specifications.

**"A 3-Period, Single-Dose, Crossover Study in Healthy Adult Subjects to Establish the Bioequivalence of the 4-MG Tablet And ——— Formulations of Montelukast, and to Evaluate the Effect of Food on the Pharmacokinetics of the——— Formulation"**

| | |
|---|---|
| Study Protocol 183 | |
| Study Initiation Date (FPI): | Jun 03, 2000 |
| Study Completion Date (LPO): | Jul 7, 2000 |
| Investigator Name/Affiliation: | [ ] |
| Clinical Study Report Date | Aug 20, 2001 |

## OBJECTIVE

- To demonstrate the bioequivalence (as determined by the AUC0-inf of montelukast) of the chewable tablet (Formulation I) and ——— (Formulation II) formulations (fasted) of montelukast.
- To compare the montelukast Cmax of the chewable tablet and ——— formulations (fasted) of montelukast.
- To evaluate the montelukast half-life AUC0-inf, Cmax, time of maximum observed plasma concentration (Tmax), and t½ obtained after administration of the chewable tablet and ——— formulations (fasted) of montelukast.
- To evaluate the plasma concentration profiles of the ——— formulation of montelukast when administered with and without food.
- To assess the general safety and tolerability of montelukast chewable tablet and ———formulations.

## SUBJECTS

Thirty one subjects (20 men [age range: 19-43 years] and 11 women [age range: 21-44 years]) met the inclusion criteria and were randomized. All subjects completed the study. Twenty-two (22) subjects were white, six were black and three were Hispanic.

## STUDY DESIGN AND TREATMENT ADMINISTRATION

This was an open-label, randomized, balanced, 3-period, crossover study conducted in healthy adult volunteers. Subjects were randomized to receive the following treatments:

**Treatment A**: single 4-mg dose of the chewable tablet in the fasted state
**Treatment B**: a single 4-mg dose of the ———formulation in the fasted state
**Treatment C**: a single 4-mg dose of the ——— formulation after consumption of a high-fat breakfast.

All fasted subjects received each of 3 single-dose treatments of montelukast, administered in separate periods as determined by a computer-generated random allocation schedule. Each treatment was separated by a washout period of at least 96 hours. Each ingestion of the appropriate test product was followed by 250 mL of water. The subject consumed a high-

fat breakfast consisting of the following: 2 large fried eggs, 1 slice of toasted white bread with 2 pats of butter, 2 strips of bacon, 240 cc of whole milk, and 4 oz. hash brown potatoes. The breakfast was consumed within 20 minutes.

## FORMULATION

The following formulations and batch numbers where used in this study.

**Table 1.** Montelukast formulation used in this study

| Test product | Potency | Formulation | Batch number | Formulation Number |
|---|---|---|---|---|
| Montelukast | 4 mg | [illegible] | CA-A870 | MR-4218 |
| Montelukast | 4 mg | Chewable tablet | CA-A870 | MR-4279 |

**Table 1a. Market Composition, Montelukast Sodium oral Granules, 4-mgand 4mg chewable tablets**

| Ingredient (mg) | 4-mg Chewable Tablet | 4-mg [illegible] |
|---|---|---|
| Montelukast sodium | | |
| [illegible] | | |
| Mannitol, USP | | |
| Microcrystalline cellulose, NF | | |
| Hydroxypropyl cellulose, NF | | |
| Red Ferric Oxide, NF | | |
| [illegible] | | |
| Cherry flavor | | |
| Aspartame, NF | | |
| Magnesium stearate, NF | | |
| Total Weight | 240.0 mg | 500.0 mg |

## PHARMACOKINETIC MEASUREMENTS

### Blood sampling

Blood samples were taken at 0.0 hr (pre-dose) and at 0.5, 1, 1:5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after administration of treatments and were for montelukast concentrations.

### Analytical Method

Plasma concentrations of montelukast were determined by HPLC-assay procedure with fluorescence detection.

## DATA ANALYSIS

### Pharmacokinetic Analysis

The major pharmacokinetic parameters such as Cmax, $AUC_{0\rightarrow\infty}$ and Tmax were derived after single dose administration using non-compartmental methods.

**Statistical Analysis**

Bioequivalence of the chewable tablet and the ——— formulation was demonstrated by comparing the 90% confidence intervals (CIs) of the GMRs for AUC0-inf and Cmax against an interval of (0.80, 1.25) identified to establish bioequivalence.

Summary statistics were calculated and the p-values from the analysis of variance (ANOVA) were also compared. The Tmax and t1/2 were evaluated by obtaining summary statistics and the p-values from the ANOVA model.

To assess the effect of food, plasma concentration profiles of the ——— formulation when administered with and without food were evaluated. Additionally 90% CIs of the GMRs for AUC0-inf and Cmax were computed, although it was not hypothesized that these would conform to the boundaries for bioequivalence.

## SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, 12-lead ECGs, and vital sign evaluations.

## RESULTS

### Analytical Method Pre-Study Validation

**Recovery:** Not included in this submission

**Limit of Quantitation:** Not mentioned in this submission

**Stability:** Not included in this submission

**Table 2.** Assay performance (in-study validation) for montelukast

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: ——— |
| **Accuracy** | Satisfactory: ——— |
| **Presicion** | Satisfactory ——— |
| **Specificity** | Satisfactory: ——— |

### Pharmacokinetic Results

The mean plasma concentration-time profiles for montelukast in healthy adult subjects receiving a single 4-mg oral dose of chewable tablet and ——— formulations of montelukast in the fasted state and with a high fat meal are shown in Figure 1. Table 1 summarizes the pharmacokinetics of montelukast for these three treatments. Individual values of Cmax and AUC0-inf for the treatments are presented in Figures 2 and 3, respectively.

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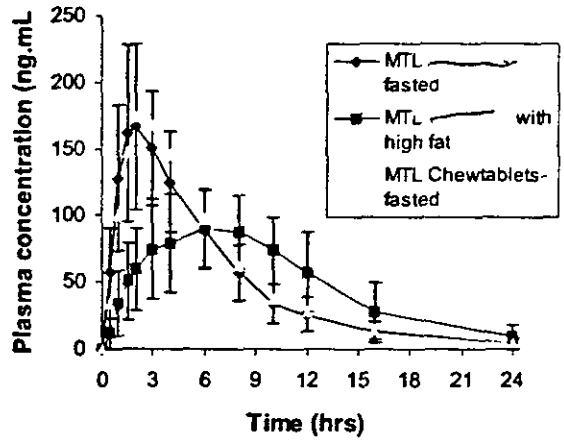


**Figure 1.** Mean Montelukast plasma concentration-time profiles following single administration of MTL ——— 4 mg-fasted, MTL - - - 4 mg with a high fat meal and MTL chewable tablets-fasted 4 mg to healthy adult volunteers. Bars represent ±SD.

**Table 3.** Mean (±SD) montelukast pharmacokinetic parameters following single administration of MTL ——— 4 mg-fasted, MTL - - - 4 mg with applesauce-fasted and MTL chewable tablets-fasted 4 mg to healthy adult volunteers.

| | Montelukast formulations | | |
|---|---|---|---|
| **PK Parameter** | **Montelukast as Tablet (fasted)** | **MTL as ——— (fasted)** | **MTL as ———(high fat)** |
| $AUC_{0-\infty}$ (ng*hr/mL) | 1271±416 | 1206±391 | 1247±404 |
| Cmax (ng/mL) | 199±59 | 184±58 | 115±24 |
| Tmax (hr) | 2.5±1.1 | 2.3±1.0 | 6.4±2.9 |
| T1/2* | 3.9 | 4 | 4.1 |

* Harmonic mean

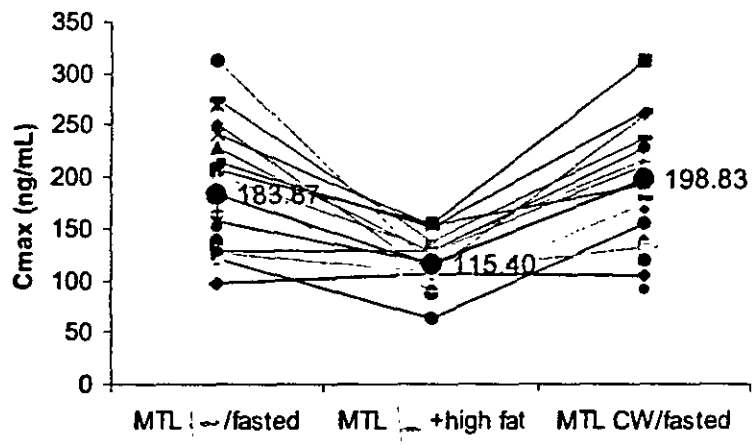


**Figure 2.** Individual montelukast Cmax values following single administration of MTL ——— 4 mg-fasted (MTL -), MTL - - - 4 mg with a high fat meal (MTL + high fat) and MTL chewable tablets-fasted 4 mg (MTL CW) to healthy adult volunteers.

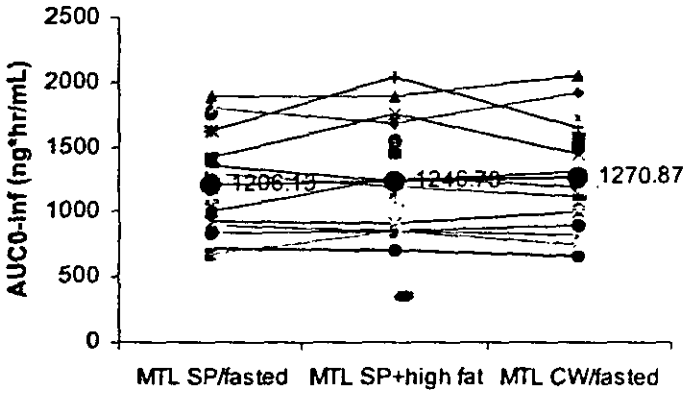


**Figure 3.** Individual montelukast AUC0-inf values following single administration of MTL ——: 4 mg-fasted (MTL —, MTL —— 4 mg with applesauce-fasted (MTL — AS) and MTL chewable tablets-fasted 4 mg (MTL CW) to healthy adult volunteers.

**Table 6.** Point estimates and 90% confidence intervals for the log-transformed Cmax and AUCinf comparing the with and without a high fat meal and the —— and the chewable tablet

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings | This reviewer's findings | Sponsor's findings | This reviewer's findings |
| MTL —— MTL Chewable tablet | AUCinf | 0.95 | 0.985 | 0.91-0.99 | 0.936-1.035 |
| | Cmax | 0.92 | 0.92 | 0.84-1.01 | 0.837-1.01 |
| MTL —— fasted/MTL —— with high fat meal | AUCinf | 1.04 | 1.04 | 0 99-1.09 | 0.987-1.09 |
| | Cmax | 0.64 | 0.65 | 0.59-0.71 | 0.59-0.71 |

## DISCUSSION

The effect of food on the BA of Montelukast delivered from the film-coated tablet and chewable formulations has been studied in the past. While food did not effect Cmax and AUC for the film coated formulation, it did have similar effect as the one observed in the present case for the — formulation. Food decreased Cmax 488 ng/mL ±66 (fasting ) to 256 ng/mL ±82 (fed) and decreased $F_{abs}$ from 73% (fasting) to 63% (fed) (data from NDA 20-830 submitted on 02/24/97). Although the effect of food on the Cmax of the chewable formulation was statistically significant, it was decided that this effect was not clinically relevant (clinical trial conducted without regards to meals or timing of food ingestion did not show any safety of efficacy concerns) and therefore, the finding were not reflected in the label

## CONCLUSION

- The Singulair —— formulation is equivalent to the Singulair chewable formulation.
- Food did not affect the AUC of montelukast delivered from the —— formulation, however food did decrease Cmax by 35% and change Tmax from 2.3 hrs to 6.4 hrs. The effect of food on the Cmax of the Singulair—— formulation might be

clinically irrelevant.

**DISSOLUTION**

The dissolution of montelukast sodium oral granules, 4 mg is carried out in an ——— medium containing ——— w/v of the ——— using USP apparatus I (baskets with 100 mesh) at a speed of 50 rpm. The amount of montelukast sodium released at the prescribed timepoint(s) is determined by HPLC using conditions, which rapidly and reliably quantitate the levels of active in the dissolution medium. The HPLC method has been validated for accuracy, injection and method precision, linearity, selectivity, solution stability and robustness.

Dissolution Parameters

| | |
|---|---|
| Apparatus: | No. 1 (baskets with 100 mesh) |
| Rotation Speed: | 50 rpm |
| Dissolution Medium: | ——— |
| Medium Volume: | ——— |
| Medium Temperature: | ——— |
| Sampling Volume: | ——— |
| Sampling Time: | ——— |

**Specification**: Q= ——— in 20 minutes

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The following table shows the results of the dissolution test for the batch used in this PK study. The product meet dissolution specifications.

**Table 1d. Dissolution data for Singulair : [redacted] formulation batch number MR-4218**

| 10min | 15min | 20min | 30min |
|---|---|---|---|
| [redacted] | | | |
| Mean | Mean | Mean | Mean |
| 102 | 102 | 102 | 102 |

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**"An Open, Randomized, 3-Period, Crossover Study to Determine the Bioequivalence of the Chewable and [redacted] Formulations of Montelukast (MK–0476) in Healthy Adult Volunteers**

**Study Protocol 090**

| | |
|---|---|
| Study Initiation Date (FPI): | 26-Mar-1999 |
| Study Completion Date (LPO): | 22-Apr-1999 |
| Investigator Name/Affiliation: | [redacted] |
| | [redacted] |
| Clinical Study Report Date | 12-Apr-2001 |

## OBJECTIVE

- To demonstrate bioequivalence between the [redacted] and chewable formulations of montelukast in the fasted state.
- To compare the plasma concentration profiles of the montelukast [redacted] formulation when given with and without applesauce in the fasted state.
- To evaluate the tolerability of single oral doses of montelukast given as a [redacted] formulation.

## SUBJECTS

Twenty-four subjects (9 men [age range: 24 to 43 years] and 15 women [age range:27 to 44 years]) met the inclusion criteria and were randomized. All subjects completed the study. Twenty-two (22) subjects were Hispanic one was white and one was black.

## STUDY DESIGN AND TREATMENT ADMINISTRATION

This was an open-label, randomized, balanced, 3-period, crossover study conducted in healthy adult volunteers. Subjects were randomized to receive the following treatments:

- One pouch of 4-mg [redacted] (Treatment A)
- One pouch of 4-mg [redacted] to be delivered on 2 teaspoons of applesauce (Treatment B)
- One 4-mg CT (Treatment C)

All fasted subjects received each of 3 single-dose treatments of montelukast, administered in separate periods as determined by a computer-generated random allocation schedule. Each treatment was separated by a washout period of at least 96 hours. Each ingestion of the appropriate test product was followed by 250 mL of water.

## FORMULATION

The following formulations and batch numbers where used in this study.

Table 1. Montelukast formulation used in this study

| Test product | Potency | Formulation | Control number | Formulation Number |
|---|---|---|---|---|
| Montelukast | 4 mg | [redacted]/pouch | WP-E431 | MR-3808 |
| Montelukast | 4 mg | Chewable tablet | WP-E432 | MR-3779 |

## PHARMACOKINETIC MEASUREMENTS

### Blood sampling

Blood samples were taken at 0.0 hr (pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 16 hours after administration of treatments and were for montelukast concentrations.

### Analytical Method

Plasma concentrations of montelukast were determined by HPLC assay procedure with fluorescence detection.

## DATA ANALYSIS

### Pharmacokinetic Analysis

The major pharmacokinetic parameters such as Cmax, $AUC_{0\rightarrow\infty}$ and Tmax were derived after single dose administration using non-compartmental methods.

### Statistical Analysis

The oral montelukast pharmacokinetic parameters (AUC(0-inf), Cmax, Tmax, and t½) were analyzed using an ANOVA model appropriate for a 3-period crossover design containing factors for subject, period, and treatment.

Within-subject coefficients of variation (CVs) and between-treatment p-values were also obtained from this ANOVA model.

For AUC(0-inf) and Cmax, the GMRs of montelukast 4-mg [redacted] to CT and 4-mg [redacted] + applesauce to 4-mg [redacted] and the corresponding 90% CIs for the GMRs were also calculated. Each CI was first computed on the difference between the treatments on the natural log scale using the t-distribution and mean square error from the ANOVA model. The upper and lower limits were then exponentiated to obtain the CI for the GMR for AUC(0-inf) and Cmax.

For AUC(0-inf) and Cmax, the 90% CI for the ratio between the montelukast [redacted] and CT was then compared with the prespecified interval of (0.80, 1.25). For the secondary comparison of montelukast 4-mg [redacted] + applesauce to 4-mg [redacted] the 90% CI for GMR of AUC(0-inf) was compared with the prespecified interval of (0.5, 2.0).

The rank transformation was applied to Tmax. The inverse transformation was applied to t½. Appropriate summary statistics for each pharmacokinetic parameter (presented in the original scale) were also calculated.

## SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory

safety data, physical examinations, 12-lead ECGs, and vital sign evaluations.

## RESULTS

### Analytical Method Pre-Study Validation

**Recovery:** Not included in this submission
**Limit of Quantitation:** Not included in this submission
**Stability:** Not included in this submission

**Table 2.** Assay performance (in-study validation) for Montelukast

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: |
| **Accuracy** | Satisfactory: |
| **Presicion** | Satisfactory: |
| **Specificity** | Satisfactory |

### Pharmacokinetic Results

The mean plasma concentration-time profiles for montelukast in healthy adult subjects receiving a single 4-mg oral dose of chewable tablet and formulations of montelukast in the fasted state and with applesauce are shown in Figure 1. Table 3 summarizes the pharmacokinetics of montelukast for these three treatments. Individual values of Cmax, AUC0-inf and Tmax for the treatments are presented in Figures 2,3 and 4, respectively. Table 4 shows the 90% confidence intervals applied to the geometric mean ratio of the PK parameters.

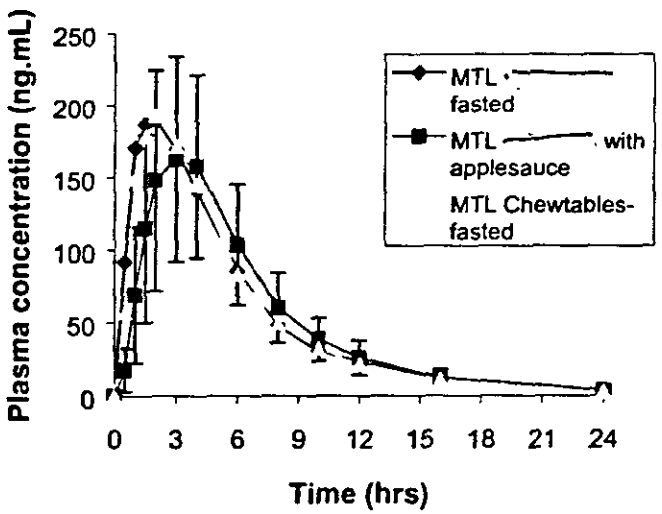


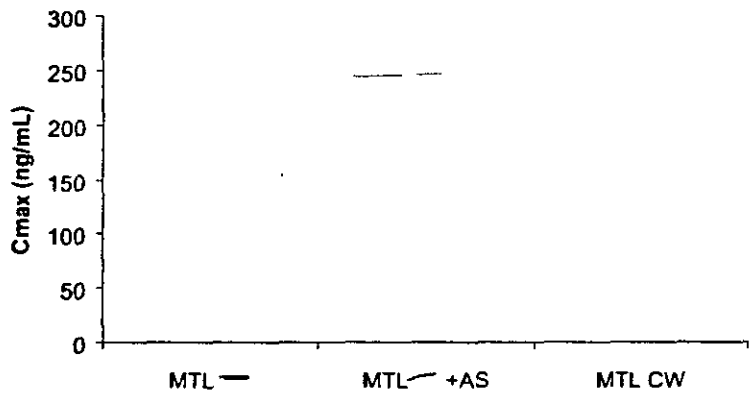

**Figure 1.** Mean Montelukast plasma concentration-time profiles following single administration of MTL 4 mg-fasted, MTL 4 mg with applesauce-fasted and MTL chewable tablets-fasted 4 mg to healthy adult volunteers. Bars represent ±SD.

**Table 3.** Mean (±SD) montelukast pharmacokinetic parameters following single administration of MTL ——— 4 mg-fasted, MTL ——— 4 mg with applesauce-fasted and MTL chewable tablets-fasted 4 mg to healthy adult volunteers.

| | Montelukast formulations | | |
|---|---|---|---|
| PK Parameter | Montelukast as ——— (fasted) | MTL as ——— with applesauce | MTL as Chewable tablets |
| $AUC_{0-\infty}$ (ng*hr/mL) | 1263±313 | 1303±408 | 1274±393 |
| Cmax (ng/mL) | 205±50.7 | 195±63.7 | 215±64.4 |
| Tmax (hr) | 2.1±1.1 | 3.4±1.2 | 2.2±0.8 |
| T1/2[a] | 4.11 | - | 4.06 |

[a]Harmonic mean

**Figure 2.** Individual montelukast Cmax values following single administration of MTL ——— 4 mg-




fasted (MTL — , MTL ——— 4 mg with applesauce-fasted (MTL — +AS) and MTL chewable tablets-fasted 4 mg (MTL CW) to healthy adult volunteers.

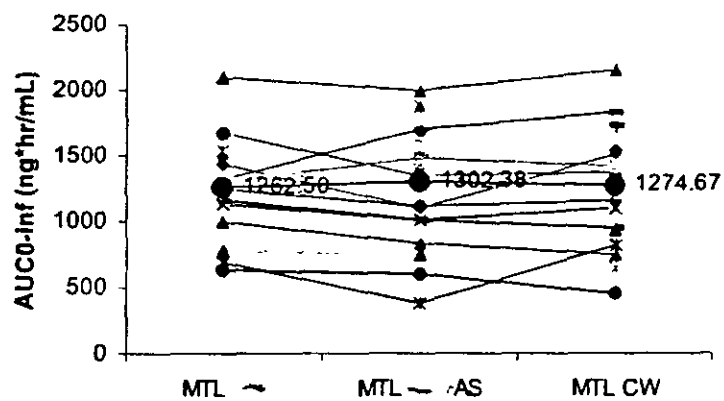



**Figure 3.** Individual montelukast AUC0-inf values following single administration of MTL ——— 4 mg-fasted (MTL — , MTL ——— 4 mg with applesauce-fasted (MTL — +AS) and MTL chewable tablets-fasted 4 mg (MTL CW) to healthy adult volunteers.

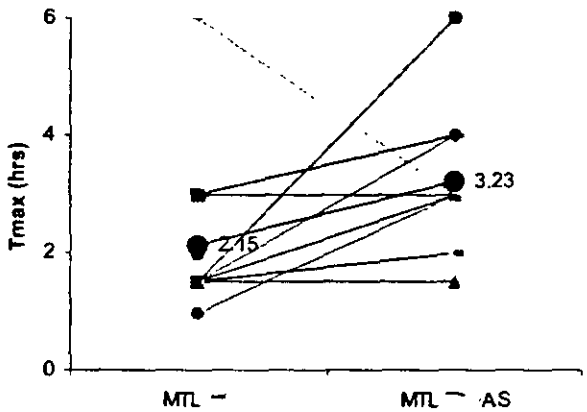



**Figure 4.** Individual montelukast Tmax values following single administration of MTL 4 mg-fasted (MTL and MTL 4 mg with applesauce-fasted (MTL AS) to healthy adult volunteers.

**Table 4.** Point estimates and 90% confidence intervals for the log-transformed Cmax and Acing comparing the with and without applesauce and the and the chewable tablet

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings | This reviewer' findings | Sponsor's findings | This reviewer' findings |
| MTL MTL Chewable tablet | Acing | 1.01 | 1.01 | 0.92-1.11 | 0.92-1.109 |
| | Cmax | 0.99 | 0.986 | 0.86-1.13 | 0.856-1.13 |
| MTL fasted/MTL with applesauce | Acing | 1.0 | 1.00 | 0.92-1.1 | 0.90-1.097 |
| | Cmax | 0.92 | 0.919 | 0.80-1.06 | 0.798-1.058 |

## CONCLUSION

- The Singulair formulation was bioequivalent to the Singulair chewable formulation (4mg CW tablet).
- Applesauce did not affect the bioavailability of montelukast delivered from the Singulair formulation.

## DISSOLUTION

The dissolution of montelukast sodium oral granules, 4 mg, is carried out in an ——— medium containing —— w/v of the ——————————, using USP apparatus I (baskets with 100 mesh) at a speed of 50 rpm. The amount of montelukast sodium released at the prescribed timepoint(s) is determined by HPLC using conditions, which rapidly and reliably quantitate the levels of active in the dissolution medium. The HPLC method has been validated for accuracy, injection and method precision, linearity, selectivity, solution stability and robustness.

Dissolution Parameters
Apparatus: No. 1 (baskets with 100 mesh)
Rotation Speed: 50 rpm
Dissolution Medium: ————————
Medium Volume: ———
Medium Temperature: ———
Sampling Volume: ———
Sampling Time: ———

**Specification**: Q=—— in 20 minutes

Table below shows the result of the dissolution data gathered from the —— batch used in this study. These data shows that this batch of ——— meets dissolution specifications.

Table D1. Dissolution data from Singulair —— batch number MR-3808

| 10 mun | 15 mun | 20 min | 30 min |
|---|---|---|---|
| | | | |
| Mean | Mean | Mean | Mean |
| 73 | 98 | 99 | 99 |

## "AN OPEN, SINGLE-DOSE, MULTICENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PLASMA CONCENTRATION PROFILES OF MONTELUKAST ———— IN 6- TO 24-MONTH-OLD CHILDREN"

**Study Protocol 136/138**

| | |
|---|---|
| Study Initiation Date (FPI): | Jan 17, 2000 |
| Study Completion Date (LPO): | May 25, 2001 |
| Investigator Name/Affiliation: | Multicenter study |
| Clinical Study Report Date | Aug 17, 2001 |

### OBJECTIVE

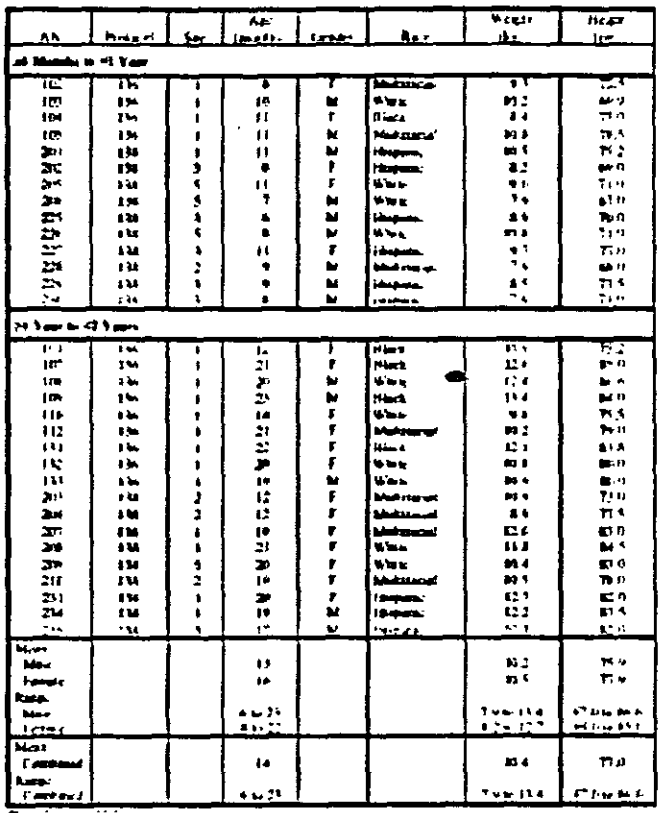
- To evaluate and compare montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax, estimated C24hrr, and apparent elimination t½) obtained from ≥6- to <12-month-, ≥12- to <24-month-, and ≥6- to <24-month-old children after administration of a 4-mg dose of the ———— formulation of montelukast with historical data in adult subjects after administration of a 10-mg dose of the FCT of montelukast.
- To evaluate and compare montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax, estimated C24hr, and apparent elimination t½) between ≥6- to <12-month-, ≥12- to <24-month-, and ≥6- to <24-month-old children after administration of a 4-mg dose of the ———— formulation of montelukast.
- To evaluate the safety and tolerability of a 4-mg (and/or either a 2-mg or 6-mg) dose of the ————formulation of montelukast in =6- to <24-month-old children.

### SUBJECTS

The demographic characteristics and patient accounting for this study is described in the tables below. A total of 26 patients were evaluable for pharmacokinetic analysis. Out of the 32 who received the test product, 1 did not completely consume the dose, 1 vomited shortly after test product administration, 2 did not have their 12-hour blood samples obtained and 2 were excluded due to modeling limitations.

| | Age-Specific Group | |
|---|---|---|
| | ≥6 Months to <1 Year | ≥1 to <2 Years |
| PATIENTS: | | |
| ENTERED. Total | 14 | 18 |
| Male (age range, months) | 9 (6 to 11) | 5 (17 to 23) |
| Female (age range, months) | 5 (8 to 11) | 13 (12 to 22) |
| COMPLETED. | 13 | 17 |
| DISCONTINUED. Total | 1 | 1 |
| Clinical adverse experience | 1 | 0 |
| Laboratory adverse experience | 0 | 0 |
| Other | 0 | 1* |

* The patient was lost to follow-up but completed the pharmacokinetic sampling and was included in the pharmacokinetic and safety analyses, except for the poststudy safety evaluation.



## STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a multicenter, open-label, single-dose study in ≥6-month- to <2-year-old patients. A single 4-mg dose of the [redacted] formulation of montelukast was administered to each patient with 1 tablespoon of applesauce. Subjects received the following treatments in a randomized fashion:

- One pouch of 4-mg [redacted] to be delivered on 1 teaspoons of applesauce

Patients were allowed to consume clear apple juice approximately 1 hour prior to administration of test product. Water was consumed ad libitum. There were no food restrictions other than ensuring that meals did not interfere with clinical procedures.

## FORMULATION

The following formulations and batch numbers where used in this study.

**Table 1.** Montelukast formulation used in this study

| Test product | Potency | Formulation | Control number | Formulation Number |
|---|---|---|---|---|
| Montelukast | 4 mg | [redacted]/pouch | CA-A678, CA-A704B, CA-A704, CA-A704D | MR-3808 |

## PHARMACOKINETIC MEASUREMENTS

### Blood sampling

Blood samples for pharmacokinetic analysis were obtained up to 24 hours after drug administration according to 1 of 2 possible fixed, 4-time point sampling schedules (Schedule A or B, Table below). The sampling schedule used in this study was selected based on a more extensive (13-time point) sampling schedule employed after administration of a single 4-mg dose of the ——— formulation of montelukast in adult subjects (Protocol 090; N=24).

| Treatment | Test Product/Dose | Number of Doses | Blood Sampling Times |
|---|---|---|---|
| A | ——— formulation of montelukast, 4 mg | 1 | 0 (predose) and 2.5, 5, and 12 hours postdose |
| B | ——— formulation of montelukast, 4 mg | 1 | 0 (predose) and 3, 8, and 24 hours postdose |

### Analytical Method

Plasma concentrations of montelukast were determined by HPLC assay procedure with fluorescence detection.

## DATA ANALYSIS

### Pharmacokinetic Analysis

The primary pharmacokinetic parameters of montelukast evaluated in this study were determined by population analysis and included the estimates: area under the concentration-time curve (AUCpop), Cmax, Tmax and t½. The sponsor estimated all PK parameters using a nonlinear mixed-effects model except for t½, where a linear mixed-effects model was used. A 1-compartment model with first-order absorption and elimination was used to fit the concentration-time data, with the log clearance parameter and log elimination rate constant constraints assumed to be randomly distributed around a population mean.

## REVIEWER'S REMARKS

The sponsor used the SAS software to estimate the population PK of the drug. This reviewer used NONMEM software to reproduce the results submitted in this NDA. This reviewer fitted the adult and children data separately and together.

When all the data was pool together, a 2-compartment model with first order absorption and elimination was used. The effect of covariates, such as weight and age were introduced into the basic adult and children model, and was evaluated based on the change in value of the objective function. Body weight was the only covariant that affected drug clearance (data not shown).

When data was handle separately, a 1-compartment model with first-order absorption and elimination was used to fit the concentration-time data generated in children 6 month to 2 years of age. The analysis was done with the inclusion and exclusion of subjects 101 and 132 who appear to be outliers. The exclusion of these subjects did not affect the outcome of the average population PK parameters.

The sponsor used the SAS software to estimate the population PK of the drug. This reviewer used NONMEM software to reproduce the results submitted in this NDA. Different model were fitted to the adult and children data separately and together.

When all the data was pool together, a 2-compartment model with first order absorption and elimination was used. The effect of covariates, such as weight and age were introduced into the basic adult and children model (pooled data), and was evaluated based on the change in value of the objective function. Body weight was the only covariant that affected drug clearance (data not shown).

When data was handle separately, a 1-compartment model with first-order absorption and elimination best described the concentration-time data generated in children 6 month to 2 years of age. The analysis was done with the inclusion and exclusion of subjects 101 and 132 who appear to be outliers. The exclusion of these subjects did not affect the outcome of the average population PK parameters.

A 2-compartment model with first order absorption and elimination better described the adult data from protocol 034. The adult Cmax was calculated using non-compartmental methods and the children Cmax was calculated based on the estimates of ke, ka and Vd. T1/2 has calculated using the estimated rate of elimination.

The effect of covariates, such as weight and age were introduced into the basic adult and children models. The analysis showed no correlation between Cmax or AUC and weight in the group of children ≥6 months to < 2 years of age receiving Singulair 4mg (Figure 6.1). This suggests that the dosage regimen in this group of children should not be based on weight.

This reviewer used WinNonlin in an attempt to estimate, which would be the most appropriate dose for this children population in terms of achieving similar exposure as that obtained in adults. Simulations were done using the estimated average PK parameters generated in the population PK analysis (data not shown).

## STATISTICAL ANALYSIS

The AUCpop was computed based on the population means of the above parameters and was compared with adult historical data analyzed similarly (Protocol 034, 10-mg FCT in adults). Since an interim analysis was provided, all confidence intervals (CIs) for the AUCpop ratios were calculated at a conservative 95% level of confidence, instead of at a 90% level. The 95% CI for the AUCpop ratio (pediatric/adult) was evaluated against the prespecified comparability bounds of (0.50, 2.00). Summary statistics were provided for all other parameters. Analyses for the age-specific subgroups were also performed.

## SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, 12-lead ECGs, and vital sign evaluations.

## RESULTS

### Analytical Method Pre-Study Validation

**Recovery:** Not included in this submission

**Limit of Quantitation:** Not included in this submission
**Stability:** Not included in this submission

**Table 2.** Assay performance (in-study validation) for Montelukast

| | Montelukast |
|---|---|
| **Linearity** | Satisfactory: |
| **Accuracy** | Satisfactory: |
| **Presicion** | Satisfactory: |
| **Specificity** | Satisfactory: |

## Pharmacokinetic Results

The individual observed and predicted plasma concentration-time profiles for montelukast in children ≥ 6month to < 2 years of age receiving a single 4-mg oral dose of the MTL ——— formulation are shown in Figure 1. Figures 2 and 3 show the relationship between AUCpop and weight and between WRES and Predicted concentration, respectively for this children population. For the adult population this relationships are shown if Figures 4 and 5.

Table 3 summarizes the finding for the model building procedure in the children and adult populations. This table shows that neither the adult clearance nor the children clearance is affected by covariates such as age and weight factors.

Table 4 summarizes the mean population pharmacokinetic parameters calculated based on individual estimations of ka, ke, CL and Vd values using NONMEM. Likewise Table 5 shows the population PK parameters calculated by the sponsor. Table 6 shows the 90% confidence intervals applied to the log-transformed Cmax and AUC comparing different children populations to adults receiving montelukast.

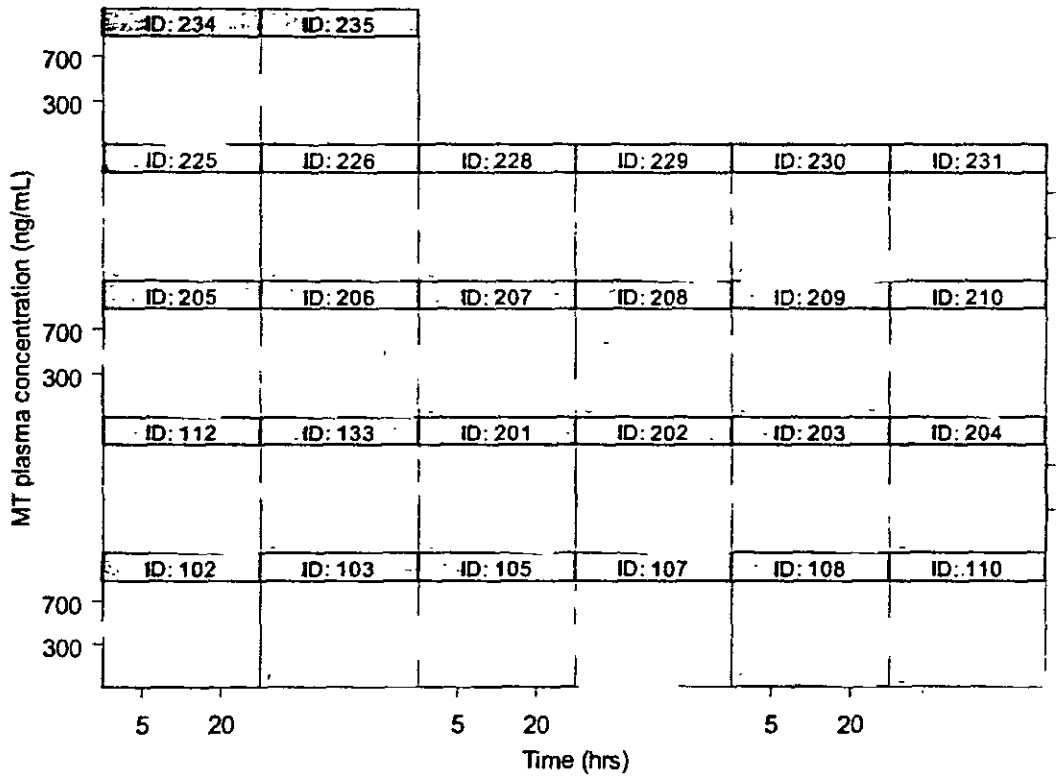



**Figure 1.** Individual Montelukast plasma concentration-time profiles following single administration of MTL ——— 4 mg to asthmatic children ≥6 months to 2 years of age.

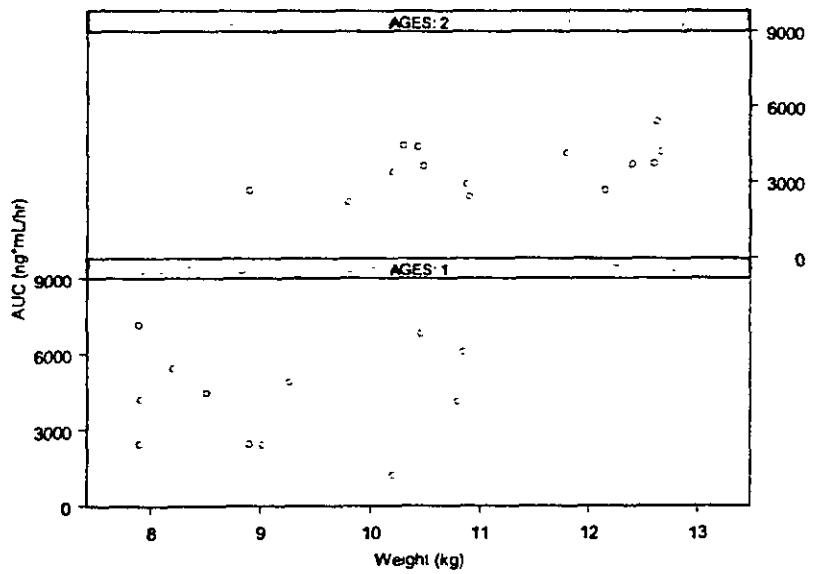



**Figure 2.** Individual AUC vs. WT in children receiving single dose of Montelukast ——— : 4 mg. Ages 1 correspond to children ≥6 months < 1 year and ages 2 correspond to children ≥ 1 years to <2 years of age.

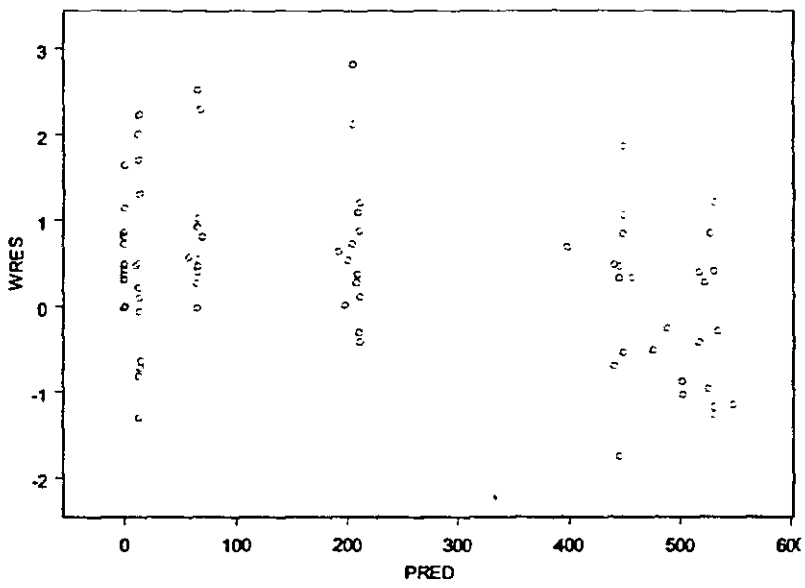



**Figure 3.** WRES vs. predicted values (PRED) in children receiving single dose of Montelukast ——— 4 mg.

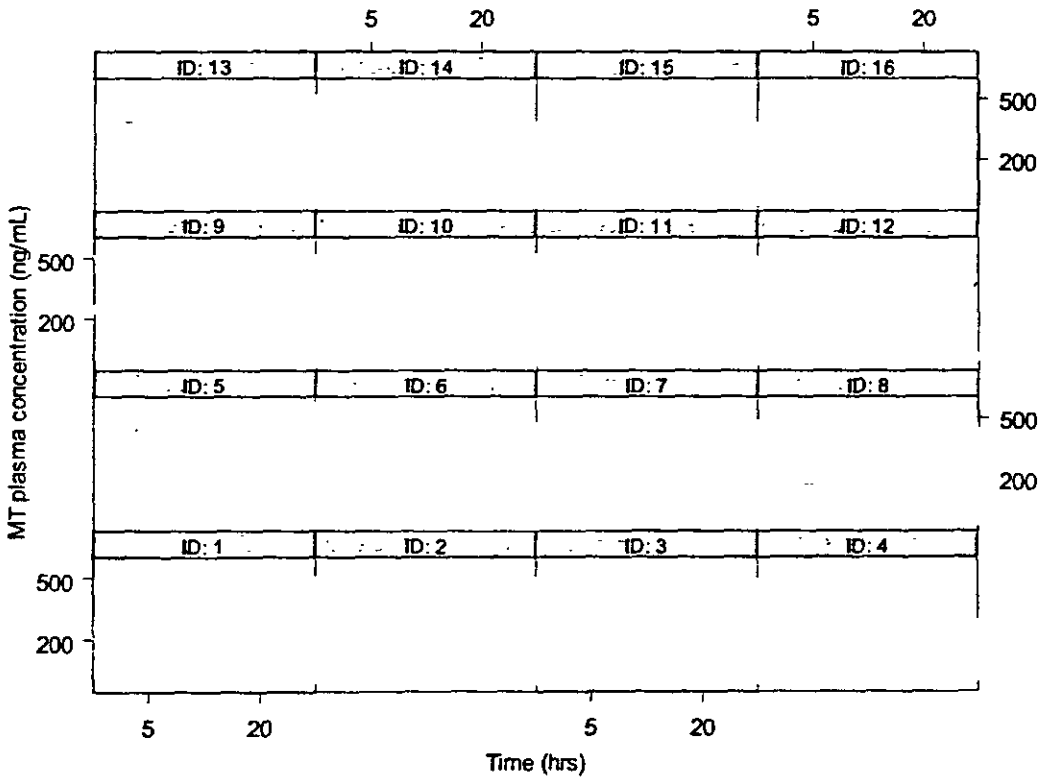



**Figure 4.** Individual Montelukast plasma concentration-time profiles following single administration of MTL film-coated tablets 10 mg to healthy adult volunteers. Data was fitted to a 2-compartment model with first order absorption and elimination. Data from protocol 034.

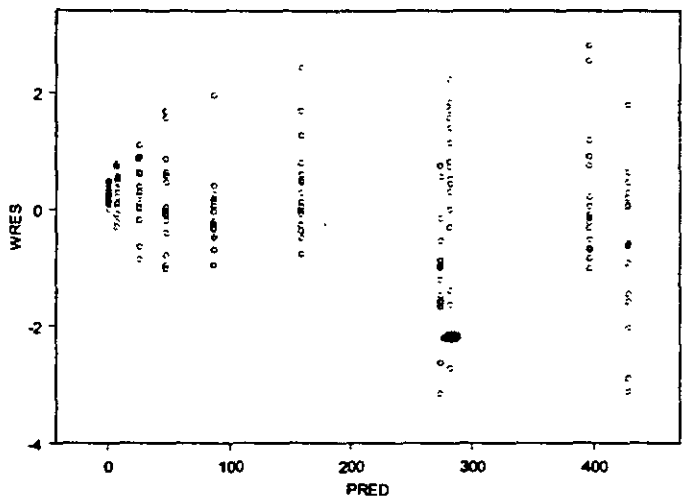



**Figure 5.** Weight of residuals versus predicted concentration plasma concentration-time profiles following single administration of MTL film-coated tablets 10 mg to healthy adult volunteers. Data was fitted to a 2-compartment model with first order absorption and elimination. Data from protocol 034.

**Table 3. Model building results**

| | Children data | | |
|---|---|---|---|
| **Model** | **OBF** | **Δ OBF** | **KEEP** |
| **Basic 1CBM** | 734.185 | | Yes |
| **Basic :CL+ WT** | 734.19 | 0 | NO |
| **Basic:CL+AGE** | 734.084 | 0.101 | NO |
| | **Adult data** | | |
| **Basic 2CBM** | 1201.45 | | YES |
| **Basic:CL+WT** | 1201.3 | 0.15 | NO |
| **Basic:CL+AGE** | 1201.35 | 0.1 | NO |

**Table 4.** Mean montelukast population pharmacokinetic parameters following single administration of Singulair——— 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM.

| **Montelukast formulations: ——— , chewable tablets, film-coated tablets** | | | | | |
|---|---|---|---|---|---|
| **PK Parameter** | **Children ≥6m to <1y** | **Children ≥1yto <2y** | **Children ≥6m to <2y** | **Children ≥2y to <6y** | **Adults** |
| $AUC_{pop}$ (ng*hr/mL)[a] | 4298.2±542.1 | 4060.4±401.9 | 3907 ±286.4 | 2761.1±200.7* | 2644.8±154.1 |
| $Cmax_{pop}$ (ng/mL)[a] | 666.6±77.9 | 561.9±47.4 | 610.2 ±44.4 | 504.4±46.1* | 352.6±25.53** |
| $CL_{pop}$ (ml/min)[a] | 20.47±4.1 | 19.59±1.33 | 19.96±1.86 | 25.7±1.58* | 66.7±18.75 |
| Tmax (hr)[b] | 1.5±0.2 | 1.52±0.16 | 1.51±0.18 | 1.81±0.78 | 3.87±1.36** |
| T1/2[b] | 3.39±1.5 | 3.37±0.97 | 3.38±1.22 | 2.36±0.9 | 1.94±0.33[c] |

[a] mean ± SE; [b]mean±SD; *Data estimated using NONMEM from protocol no. 066; **calculated using non-compartmental methods; [c]based on 2CBM parameters

**Table 5.** Mean montelukast population pharmacokinetic parameters following single administration of Singulair ——— 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by sponsor

| | Montelukast formulations: ———chewable tablets, film-coated tablets | | | | |
|---|---|---|---|---|---|
| PK Parameter | Children ≥6m to <1y | Children ≥1yto <2y | Children ≥6m to <2y | Children ≥2y to <6y | Adults |
| $AUC_{pop}$ (ng*hr/mL)[a] | 3470.9±499.3 | 3039.3±212.5 | 3226.6±250 | 2721±164.4 | 2595±164.5 |
| Cmax (ng/mL)[a] | 583.5±84.8 | 470.1±40.7 | 514.4±43.1 | 471.01±65.3 | 283.7±54.3 |
| $CL_{pop}$ (ml/min)[a] | 19.2±2.8 | 21.9±1.5 | 20.7±1.6 | - | 64.9±4.2 |
| Tmax (hr)[b] | 2.07±0.28 | 2.34±0.14 | 2.24±0.14 | 2.07±0.3 | 3.39±0.2 |
| T1/2[b] | 3.24±0.36 | 3.48±0.2 | 3.39±0.2 | 3.17±0.2 | 4.09±0.17 |

[a] mean ± SE; [b]mean±SD

**Table 6**. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUC comparing different children populations to adults receiving montelukast

| Comparison | PK parameter | Point estimates | | 90% confidence intervals | |
|---|---|---|---|---|---|
| | | Sponsor's findings* | This reviewer' findings | Sponsor's findings* | This reviewer' findings |
| ≥6m to <1 y/adult | AUC | 135 | 148.1 | 102-154 | 119.3-183.9 |
| | Cmax | | 178.9 | | 141.4-226.4 |
| ≥1y to <2y/adult | AUC | 118 | 133.7 | 97-144 | 108.7-164.5 |
| | Cmax | | 157.8 | | 125.9-197.3 |
| ≥2y to <6 y/adult | AUC | 105 | 103.2 | 90-122 | 84.2-126.5 |
| | Cmax | | 141.8 | | 113.6-176 9 |

*sponsor reported 95% confidence intervals

Figures 6, 7 and 8 are box plots for the population CL, AUC and Cmax, respective for children 6 months to <5 years of age and adult volunteers. These parameters were calculated based on individual estimation of PK parameters calculated using a population PK approach. The adult Cmax individual values for calculated using non-compartmental methods.

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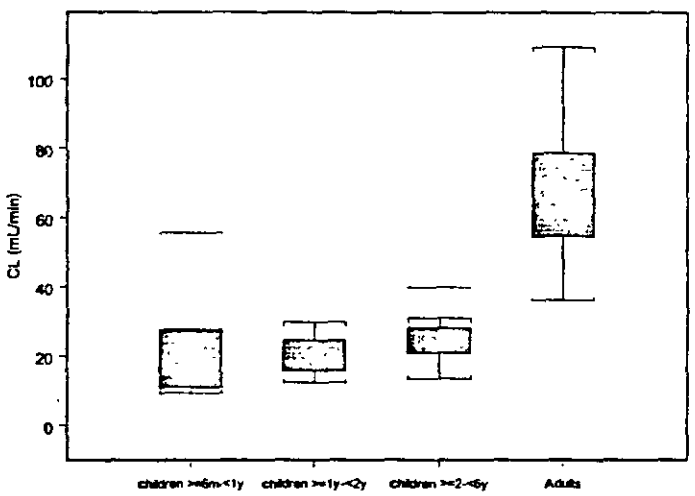


**Figure 6**. Box plot for population clearances (CL) following single administration of Singulair 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. Subjects 101 and 132 excluded from the 6m-2y old Group.

***children >=6m-<1y***
Min:
1st Qu.: 11.655000
Mean: 20.470000
Median: 14.960000
3rd Qu.: 27.315000
Max:
Std Dev.: 13.660793
SE Mean: 4.118884
LCL Mean: 11.292555
UCL Mean: 29.647445

***children >=1y-<2y***
Min:
1st Qu.: 15.895000
Mean: 19.590000
Median: 18.100000
3rd Qu.: 23.760000
Max:
Std Dev.: 5.142417
SE Mean: 1.327766
LCL Mean: 16.742224
UCL Mean: 22.437776

***children >=2-<6y***
Min:
1st Qu.: 22.550000
Mean: 25.650000
Median: 26.860000
3rd Qu.: 28.105000
Max:
Std Dev.:6.132151
SE Mean: 1.583314
LCL Mean: 22.254128
UCL Mean: 29.045872

***Adults***
Min:
1st Qu.: 55.952500
Mean: 66.675000
Median: 62.070000
3rd Qu.: 78.007500
Max:
Std Dev.: 18.751380
SE Mean: 4.687845
LCL Mean: 56.683095
UCL Mean: 76.666905

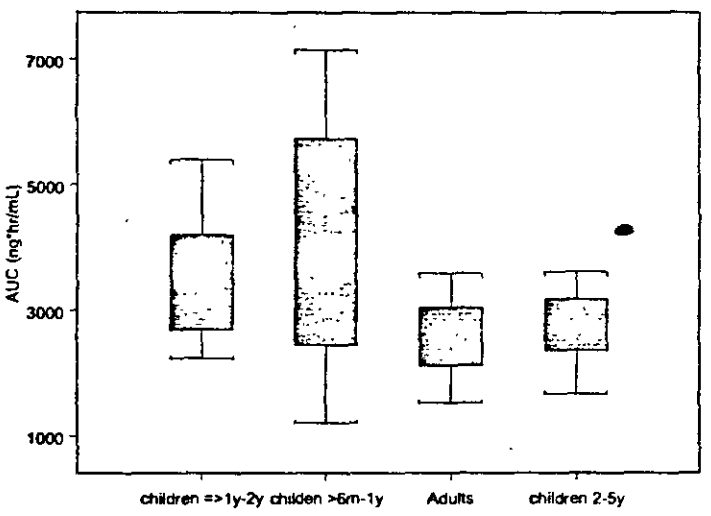


**Figure 7.** Box plot for AUC following single administration of Singulair——4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. Subjects 101 and 132 excluded from the 6m-2y old Group.

***Children =>1y-2y***
Min: ——
1st Qu.: 2752.5750
Mean: 3573.9214
Median: 3657.3500
3rd Qu.: 4190.0750
Max: ——
Std Dev.: 907.0569
SE Mean: 242.4212
LCL Mean: 3050.2024
UCL Mean: 4097.6405

***Children >6m-1y***
Min: ——
1st Qu.: 2441.325
Mean: 4295.592
Median: 4318.400
3rd Qu.: 5576.600
Max: ——
Std Dev.: 1889.144
SE Mean: 545.349
LCL Mean: 3095.287
UCL Mean: 5495.897

***Adults***
Min: ——
1st Qu.: 2137.6000
Mean: 2689.4188
Median: 2685.2500
3rd Qu.: 2982.8500
Max: ——
Std Dev.: 765.7512
SE Mean: 191.4378
LCL Mean: 2281.3787
UCL Mean: 3097.4588

***Children 2-5y***
Min: ——
1st Qu.: 2371.8000
Mean: 2761.0933
Median: 2482.4000
3rd Qu.: 2971.3000
Max: ——
Std Dev.: 777.3142
SE Mean: 200.7017
LCL Mean: 2330.6311
UCL Mean: 3191.5556

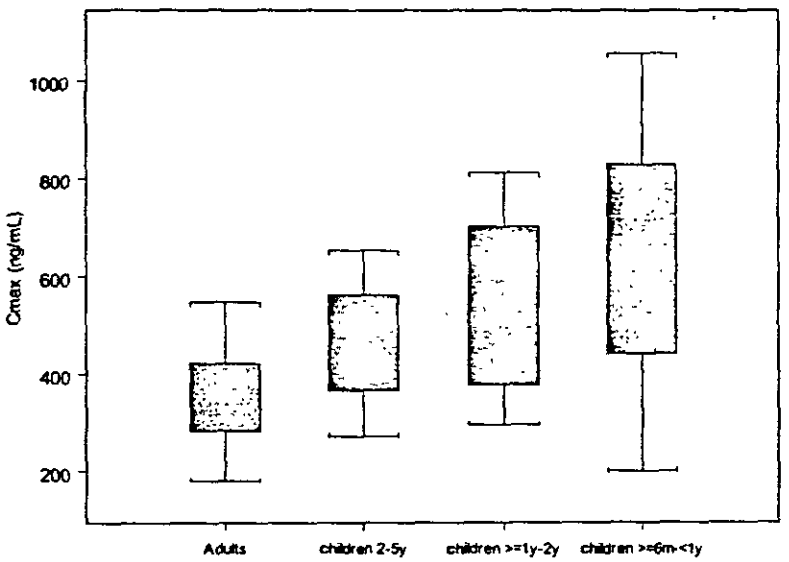


**Figure 6**. Box plot for population Cmax (CLpop) following single administration of Singulair ~~4~~ 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. The Cmax adult data was calculated using non-compartmental methods. Subjects 101 and 132 excluded from the 6m-2y old Group.

***Adults***

| | |
|---|---|
| Min: | |
| 1st Qu.: | 295.25000 |
| Mean: | 352.56250 |
| Median: | 330.50000 |
| 3rd Qu.: | 419.00000 |
| Max: | |
| Std Dev.: | 102.15476 |
| SE Mean: | 25.53869 |
| LCL Mean: | 298.12807 |
| UCL Mean: | 406.99693 |

***children 2-5y***

| | |
|---|---|
| Min: | |
| 1st Qu.: | 392.46000 |
| Mean: | 504.44267 |
| Median: | 515.19000 |
| 3rd Qu.: | 547.72500 |
| Max: | |
| Std Dev.: | 178.70098 |
| SE Mean: | 46.14039 |
| LCL Mean: | 405.48136 |
| UCL Mean: | 603.40397 |

***children >=1y-2y***

| | |
|---|---|
| Min: | |
| 1st Qu.: | 400.87500 |
| Mean: | 561.98571 |
| Median: | 571.64000 |
| 3rd Qu.: | 699.55250 |
| Max: | |
| Std Dev.: | 177.52427 |
| SE Mean: | 47.44536 |
| LCL Mean: | 459.48625 |
| UCL Mean: | 664.48518 |

***children >=6m-<1y***

| | |
|---|---|
| Min: | |
| 1st Qu.: | 465.14250 |
| Mean: | 666.55750 |
| Median: | 723.40500 |
| 3rd Qu.: | 824.71000 |
| Max: | |
| Std Dev.: | 269.83232 |
| SE Mean: | 77.89388 |
| LCL Mean: | 495.11422 |
| UCL Mean: | 838.00078 |

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## DISCUSSION

As observed in Tables 3 and 4 the estimated average population PK parameters calculated by this reviewer for the adults and 2- to 5 years olds are in agreement with the values reported by the sponsor. However, the calculated values by this reviewer for Cmax and AUC for children 6 months to <2 years of age are much higher than the ones reported by the sponsor. This discrepancy might be due to a difference in the procedure for calculating these parameters. This reviewer calculated the average population PK parameters based on the estimation of individual values. The sponsor's approach was to calculate the average population clearances and AUC based on average estimated population parameters. This speculation is supported by simulation done using the average estimated population PK parameters calculated by this reviewers, which showed similar values than those reported by the sponsor (data not shown).

As shown in Table 5 and Figures 7 and 8, the variability in the data for the 2 years to <6 year olds and adults is similar, indicating similar safety and efficacy. However, AUC and Cmax values for the 6 month to <2 year olds, especially the 6month to <1 year of age are highly variable. AUC values range from 1200 ng*hr/mL to 7153 ng*hr/mL and the mean value was 48% higher than the observed in adults. Cmax ranges from 465.1 to 1057.8 ng/ml and the mean value increase by 79% compared to adults. Higher variability in Cmax values compared to variability in AUC values has been observed in the already approved formulation for children 2 to <6 years of age whose Cmax was 42% higher compare to that observed in adults. There might be several reasons for this variability in the younger children population. One can speculate that it might be due to differences in metabolic clearance, extend of absorption, compliance, etc.

The systemic exposure in the ≥ 1 year to <2 year olds is less variable, but still higher compared to the one in adults. The mean AUC was 34% higher and mean Cmax was 58% higher that those observed in adults.

Simulations were done by this reviewer considering the estimated average PK parameters generated in the population PK analysis using WinNonlin in an attempt to estimate which would be the most appropriate dose for this children population in terms of achieving similar exposure (AUC) as that obtained in adults. It was found that 3.5-mg better compares with the AUC obtained for the adult population. However, one should keep in mind that this simulations were done considering average PK parameters which means that those patients who had a exposure of 1200 ng*hr/ml receiving 4 mg may be at risk of efficacy assuming a target exposure of efficacy between 1200 to 4500 ng*hr/mL as reported by the sponsor.

It is clear from Table 5 that the exposure in the 1-2 year olds, especially the one in the 6 months to <2 years, is significantly different that the one observed in adults. How clinical relevant are these differences in exposure needs to be evaluated by the medical reviewer.

## CONCLUSION

- It seems that clearance and therefore AUC are not correlated with weight in the group of children ≥6 months to < 2 years of age.
- High variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age. A lower

dose of Singulair ——— to this population would give more comparable average systemic exposure to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age.

**DISSOLUTION**

The dissolution of montelukast sodium oral granules, 4 mg is carried out in an ——— medium containing ——— w/v of the ; ——— using USP apparatus I (baskets with 100 mesh) at a speed of ——— The amount of montelukast sodium released at the prescribed timepoint(s) is determined by HPLC using conditions, which rapidly and reliably quantitate the levels of active in the dissolution medium. The HPLC method has been validated for accuracy, injection and method precision, linearity, selectivity, solution stability and robustness.

Dissolution Parameters
Apparatus: No. 1 (baskets with 100 mesh)
Rotation Speed: 50 rpm
Dissolution Medium: ———
Medium Volume: ———
Medium Temperature: ———
Sampling Volume: ———
Sampling Time: ———

**Specification**: Q=——— in 20 minutes

Table below shows the result of the dissolution data gathered from the ——— batch used in this study. These data shows that this batch of ——— meets dissolution specifications.

Table D1. Dissolution data from Singulair ——— batch number MR-3808

| 10 min | 15 min | 20 min | 30 min |
|---|---|---|---|
| | | | |
| Mean | Mean | Mean | Mean |
| 73 | 98 | 99 | 99 |

## Office of Clinical Pharmacology and Biopharmaceutics

*New Drug Application Filing and Review Form*

General Information About the Submission

| | Information | | Information |
|---|---|---|---|
| NDA Number | 21-409 | Brand Name | Singulair granules |
| OCPB Division (I, II, III) | II | Generic Name | Montelukast Sodium |
| Medical Division | DPADP | Drug Class | Leukotriene antagonist |
| OCPB Reviewer | Sandra Suarez-Sharp | Indication(s) | Treatment of asthma |
| OCPB Team Leader | Emmanuel Fadiran | Dosage Form | Granules |
| PM Reviewer | He Sun | Dosing Regimen | pediatric patients 6 months to 5 years of age: one packet of SINGULAIR 4-mg ——— daily |
| Date of Submission | Sep 28, 2001 | Route of Administration | oral |
| Estimated Due Date of OCPB Review | Jul 2002 | Sponsor | Merck Research Lab. |
| PDUFA Due Date | Jul 28, 2002 | Priority Classification | Standard |
| Division Due Date | Jul 14, 2002 | | |

3 Clin. Pharm. and Biopharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| STUDY TYPE | [redacted] | [redacted] | [redacted] | [redacted] |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | [redacted] | [redacted] | |
| Tabular Listing of All Human Studies | | [redacted] | [redacted] | |
| HPK Summary | X | [redacted] | [redacted] | |
| Labeling | | [redacted] | [redacted] | |
| Reference Bioanalytical and Analytical Methods | X | [redacted] | [redacted] | |
| I. Clinical Pharmacology | [redacted] | [redacted] | [redacted] | [redacted] |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | [redacted] | [redacted] | [redacted] | [redacted] |
| Healthy Volunteers- | [redacted] | [redacted] | [redacted] | [redacted] |
| single dose: | X | 3 | 3 | |
| multiple dose. | | | | |
| Patients- | [redacted] | [redacted] | [redacted] | [redacted] |
| single dose: | X | 1 | 1 | |
| multiple dose | | | | |
| Dose proportionality - | [redacted] | [redacted] | [redacted] | [redacted] |
| fasting / non-fasting single dose: | X | 1 | 1 | |
| fasting / non-fasting multiple dose. | | | | |
| Drug-drug interaction studies - | [redacted] | [redacted] | [redacted] | [redacted] |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | [redacted] | [redacted] | [redacted] | [redacted] |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | X | 1 | 2 | |
| geriatrics: | | | | |

| | | | | |
|---|---|---|---|---|
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | [redacted] | [redacted] |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | [redacted] | [redacted] |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | [redacted] | [redacted] |
| Data rich: | | | | |
| Data sparse: | X | 1 | 3 | |
| **II. Biopharmaceutics** | | | [redacted] | [redacted] |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | [redacted] | [redacted] |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | [redacted] | [redacted] |
| traditional design; single / multi dose: | X | 1 | 1 | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | X | 1 | 1 | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |
| **BCS class** | | | | |
| **III. Other CPB Studies** | | | [redacted] | [redacted] |
| **Genotype/phenotype studies:** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | 4 | 5 | |

| | | |
|---|---|---|
| **Filability and QBR comments** | | |
| | **"X" if yes** | **Comments** |
| Application filable ? | **X** | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one" |
| Comments sent to firm ? | **X** | Comments have been sent to firm (or attachment included). FDA letter date if applicable.<br>**1. Provide chemical stability of the Singulair [redacted] formulation in applesauce.**<br>**2. If possible provide dissolution profiles of the Singulair [redacted] formulation.**<br>**3. Provide data files, control stream files and output NONMEM files generated from protocol 136/138 (population pharmacokinetics in children 6 months to 2 years of age.**<br>**4. Provide data files, control stream files and output NONMEM files generated for children 2-5 years of age receiving 4mg chewable tablets.**<br>**5.** |
| QBR questions (key issues to be considered) | **1. Is the [redacted] granule formulation equivalent to the approved chewable formulation?**<br>**2. Does food affect the BA of montelukast from the [redacted] formulation?**<br>**3. Does applesauce affect the BA of montelukast from the [redacted] formulation?**<br>**4. Is the systemic exposure of montelukast from the [redacted] formulation proportional to dose?**<br>**5. Does the PK data support the dosage regimen in children 2 years of age?** | |
| Other comments or information not included above | This reviewer will review the population PK study with the guidance of He Sun (PM reviewer). | |
| Primary reviewer Signature and Date | | |
| Secondary reviewer Signature and Date | | |

CC: NDA 21-409, HFD-870 (Electronic Entry or Lee), HFD-570 (Yu), HFD-870 (Fadiran, Sun, Hunt, Malinowski)), CDR (B. Murphy)

APPEARS THIS WAY
ON ORIGINAL

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/s/
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Sandra Suarez
7/10/02 09:30:08 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
7/10/02 10:17:05 AM
BIOPHARMACEUTICS
I concur

# ADDENDUM TO REVIEW

**NDA No.:** 21-409

**Drug Name:** Singulair (Montelukast) Oral Granules

**Submission Date:** September 28, 2001

**Review Completion Date:** July 25, 2002

**Subject:** Revision of AUC Ratios in the Carcinogenesis and Overdose sections of the labeling. An addendum to Dr. Luqi Pei's Review dated the July 19, 2002

This addendum revises the recommended exposure ratios between animals and humans in the labeling of Singulair in the July 19, 2002 review. The following table summarizes the revision.

| Section/species | Dose (mg/kg/day) | AUC Ratios (Animal/Human) | |
|---|---|---|---|
| | | 7/19/02 Recommendation | Current Recommendation |
| Carcinogenesis | | | |
| Mouse | 100 | | 30 |
| Rat | 200 | | 90 |
| Overdose | | | |
| Mouse | 5,000 | | 250 |
| Rat | 5,000 | | 170 |

This revision was prompted by today's agreement between the Division and Merck that a revised AUC value (3.574 μg.hr/ml for children 12-23 months of age) should be used in the labeling. (The AUC ratios in the July 19, 2002 review were based on an AUC value of . . μg.hr/ml in children.) Other parameters in the calculation (i.e., animal AUC values, the method of calculation and the rounding rule) remain the same as the referred review indicates.

Luqi Pei, Ph.D.

Pharmacologist

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/s/

Luqi Pei
7/25/02 04:27:39 PM
PHARMACOLOGIST

Joseph Sun
7/25/02 04:30:44 PM
PHARMACOLOGIST
I concur.