

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-829

CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)

JAN 20 1998

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:
20-829
(Montelukast 10 mg film-coated tablets)
20-830
(Montelukast 5 mg chewable tablets)

SUBMISSION DATE:
01/12/98

BRAND NAME: Singulair

SPONSOR: Merck Research Labs.

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Sponsor's Responses

Code: 1S

TITLE: "Review of Sponsor's Responses To The Agency's Review Comments on Montelukast's NDAs"

SUMMARY:

On 02/21/97, the sponsor, Merck Research Labs, submitted NDA 20-829 (10 mg film-coated tablet) and NDA 20-830 (5 mg chewable tablet) to the Agency for review for montelukast sodium. The Human Pharmacokinetics and Bioavailability section of each of these NDAs contains identical information, i.e., 23 pharmacokinetic/bioavailability studies. These studies were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) on 01/08/98. Three comments of OCPB/DPE II were conveyed to the sponsor by fax through the CSO on 01/06/98. On 01/12/98, the sponsor submitted their responses to the Agency (Attachment 1) and the responses are reviewed.

RECOMMENDATION:

The sponsor's responses that were submitted on 01/12/98 have been reviewed by OCPB/DPE II and they were found overall acceptable.

/S/

01/15/98

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD/FT initialed by Mei-Ling Chen, Ph.D.

/S/

1/20/98

cc: NDAs 20-829 and 20-830, HFD-570 (Honig and Trontell, Kuzmik), HFD-870 (M.L. Chen, T.M. Chen), CDR (B. Murphy).

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

<u>NDA:</u>	<u>SUBMISSION DATE:</u>	
20-829 (Montelukast 10 mg film-coated tablets)	02/24/97	07/03/97
	09/23/97	10/02/97
	10/16/97	10/29/97
	11/18/97	11/26/97
20-830 (Montelukast 5 mg chewable tablets)		

BRAND NAME: SingulairSPONSOR: Merck Research Labs.REVIEWER: Tien-Mien Chen, Ph.D.TYPE OF SUBMISSION: Original NDA (New Molecular Entity, NME) Code: 1STITLE: "Review of Human Pharmacokinetics and Bioavailability for Montelukast"SUMMARY:

On 02/24/97, the sponsor, Merck Research Labs, submitted NDA 20-829 [10 mg film-coated tablet (FCT)] and NDA 20-830 [5 mg chewable tablet (CT)] to the Agency for review for montelukast sodium. Montelukast sodium is reported to bind with high affinity and selectively to cysteinyl leukotriene receptors found in the human airway without any agonist activity. It is an NME and is to be indicated for the prophylaxis and chronic treatment of asthma. The sponsor is seeking approval for two oral formulations (10 mg FCT and 5 mg CT). The recommended dosing regimens are 1x10 mg FCT for adults including adolescents (≥ 15 years) and 1x5 mg CT for children 6 and 14 years old given QD at bedtime. Please see the package insert (PI) in Attachment 1 for details.

Identical information, i.e., 23 pharmacokinetic/bioavailability (PK/Bio) studies, was submitted to the Human Pharmacokinetics and Bioavailability section of each of these NDAs. Eighteen studies are considered to be pivotal and five are supportive. The 18 pivotal PK/Bio studies reviewed are for basic PK after oral or intravenous administration (IV), in vivo metabolism (using ^{14}C -radiolabeled drug), dose proportionality, food effect, absolute bioavailability (F_{abs}), relative bioavailability (F_{rel}), morning vs. evening dose, young vs. elderly, male vs. female, single vs. multiple dose, target population (adolescent patients and pediatric patients 6-14 years old), special population (mild to moderate hepatic insufficiency), and drug-drug (D-D) interaction (with theophylline, corticosteroids, oral contraceptives, digoxin, terfenadine, warfarin, or phenobarbital). The assay methodologies, formulations, and dissolution methodologies are also reviewed. The analysis of PK/pharmacodynamic (PD) relationship, however, was

conducted in early studies using doses which exceeded the dose to be recommended in the PI.

Additionally, blood/plasma ratio, protein binding, pharmacologic activity for possible metabolites, identification of the enzyme(s) responsible for the metabolism of this drug using liver microsomes, enzyme markers and inhibitors, etc. were investigated in vitro and are reviewed. Finally, the 5 supportive PK studies are briefly reviewed as well.

RECOMMENDATION:

NDA 20-829 (montelukast sodium 10 mg FCT for adults) and NDA 20-830 (montelukast sodium 5 mg CT for children 6-14 years old) that were filed by Merck Research Labs on 02/24/97 have been reviewed by the Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the information submitted to the human PK/Bio section is acceptable from the CPB perspective. There are general comments and a labeling comment provided in pages 24-26. Finally, General Comment Nos. 7 to 10 and the Labeling Comment need to be conveyed to the sponsor ASAP.

CPB Briefing on 12/09/97:

Drs. P. Honig (MO), D. Conner, L. Lesko, S.M. Huang, J. Balain, M.L. Chen, J. Lazor, R. Miller, E. Fadiran, and R. Yuan and Mr. J. Hunt

/S/

11/26/97

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Dale P. Conner, Pharm.D.

DPC 12/01/97

FT initialed by Dale P. Conner, Pharm.D.

/S/ 1/8/98

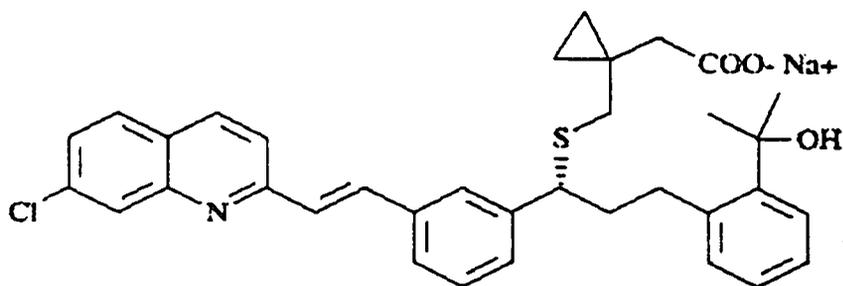
cc: NDAs 20-829 and 20-830, HFD-570 (Honig and Trontell, Kuzmik), HFD-870 (M.L. Chen, T.M. Chen), HFD-650 (D. Conner), CDR (B. Murphy).

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I. BACKGROUND:

The structural formula of montelukast sodium is shown below:



Molecular Formula: $C_{35}H_{35}ClNO_3S \cdot Na$

Molecular Weight: 608.2

Montelukast sodium is a hygroscopic, optically active, white to off-white powder and is manufactured as a trans-R-enantiomer only. It is freely soluble in water, methanol, and ethanol and practically insoluble in acetonitrile.

Montelukast is surface active and forms self-associated structures in aqueous solution. At concentrations below 5 mg/ml, where self-association is less pronounced, the free-acid form precipitates out of aqueous solution.

II. SUMMARY OF PHARMACOKINETICS, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:

Table 1: Summary of 18 Pivotal PK Studies

Protocol No.	Study Objectives/Design	Dosage Forms (Formulation No.)	No. of Subjects (M/F)
033	SD ^a IV and oral for safety and tolerability and basic PK in healthy adults	Part I: IV 3,9,18 mg Oral 10 mg FCT (HT) ^b Part II: IV 9 mg Oral 10 mg FCT (HT)	Part I: 9M Part II: 9F
021	SD PK in adolescent patients (12-17 years old)	2 mg FCT and 10 mg FCT (HT)	10M+6F
036	SD in early pubertal adolescent patients (9-14 years old)	Part I: 3x2 mg FCT Part II: 10 mg FCT (HT)	Part I: 7M+2F Part II: 4M+5F
026	Dose proportionality/timing of dose with or without snack in healthy adults	2 mg FCT, 10 mg FCT (HT), and 50 mg FCT	16M
034	4x4 SD PK in healthy adults	2 mg CT, 5 mg CT (BCT) ^c , 10 mg CT and 10 mg FCT (HT)	16M
060	5x5 SD food effect on PK in healthy adults	IV 7 mg, 5 mg CT (CCT), and 10 mg FCT (HT)	8M+2F
023	Oral ¹⁴ C-drug for ADME in healthy adults	100 mg in capsules	Part I: 3M Part II: 3 M
051	Oral ¹⁴ C-drug for biliary secretion in healthy adults	50 mg in capsules	Part I: 3M Part II: 3M
039	SD and MD ^a PK in pediatric patients (6-8 years old)	5 mg CT (BCT)	Part I: 11M+3F Part II: 3M+2F
057	SD PK in subject with hepatic insufficiency	IV 7 mg and 10 mg FCT (HT)	6M+2F
045	SD and MD PK in young adults and SD PK in healthy elderly (65-73 years old)	Part I: 10 mg FCT (HT) Part II: IV 7 mg and 10 mg FCT (HT)	Part I: 4M+8F Part II: 8M+4F
047	MD D-D on theophylline PK in healthy adults	10 mg FCT (HT) QD x 11 days and theophylline 4.65mg/kg IV	15M
012	MD D-D on prednisone and prednisolone PK in healthy adults	200 mg QD x 6 wks 20 mg of prednisone and prednisolone	10M
018	MD D-D on PK of oral contraceptives in healthy adults	100 mg QD x 8 days and Ortho's Novum (1/35) QD	22F
053	MD D-D on digoxin PK in healthy adults	10 mg FCT (HT) QD x 11 days and digoxin 0.5 mg QD x 14 days	6M+4F
055	MD D-D on warfarin PK in healthy adults	10 mg FCT (HT) QD x 12 days and warfarin 30 mg x 7 days	12M
048	MD D-D on terfenadine PK in healthy adults	10 mg FCT (HT) QD x 7 days and 60 mg terfenadine BID x 14 days	8M+5F
058	SD D-D of phenobarbital on montelukast PK in healthy adults	phenobarbital 100 mg QD x 14 days and 10 mg FCT(HT)	10M+4F

- a. Single-dose (SD) and Multiple-dose (MD).
b. Film-coated tablet (FCT) and chewable tablet (CT).
c. Drug-drug interaction study (D-D).

1. SINGLE-DOSE PHARMACOKINETICS IN HEALTHY SUBJECTS:

Single-dose study # 033 investigated montelukast PK in healthy volunteers for 1) dose proportionality (3, 9, and 18 mg) after 15 min short-term IV infusion in males, 2) tolerability and safety of a 9 mg IV dose given by 2, 5, or 15 min IV infusion to females, and 3) the F_{abs} (%) of an oral dose of 1x10 mg FCT in both genders under fasting conditions.

The study results show that 1) the geometric mean (specified otherwise) plasma concentrations at the end of infusion and the geometric mean (specified otherwise) area under the curve from time zero to infinity (AUC) values were proportional among the IV doses, 2) the mean total clearance (CL) after IV ranged from 45 to 48 ml/min for healthy volunteers, 3) the mean steady-state volume of distribution ($V_{d_{ss}}$) after IV doses was estimated to be around 10-11 liters, 4) the harmonic mean (specified otherwise) terminal half-life ($T_{1/2}$) values ranged from 4.5 to 5.5 hr after IV or oral administration, 5) the arithmetic mean time to reach peak plasma levels (T_{max}) values after oral doses ranged from 3.3 to 3.7 hr, 6) the mean oral F_{abs} value was calculated to be around 67% for male which is slightly higher than that for females (58%), and 7) no major gender differences in IV or oral PK of montelukast were found.

Some basic PK parameters (mean \pm standard deviation; SD) that were obtained from this study are summarized below in Table 2 and mean plasma levels following separate IV (9 mg) and oral (10 mg) administration are shown in Figure 1:

Table 2: Summary of PK Parameters (Mean \pm SD)

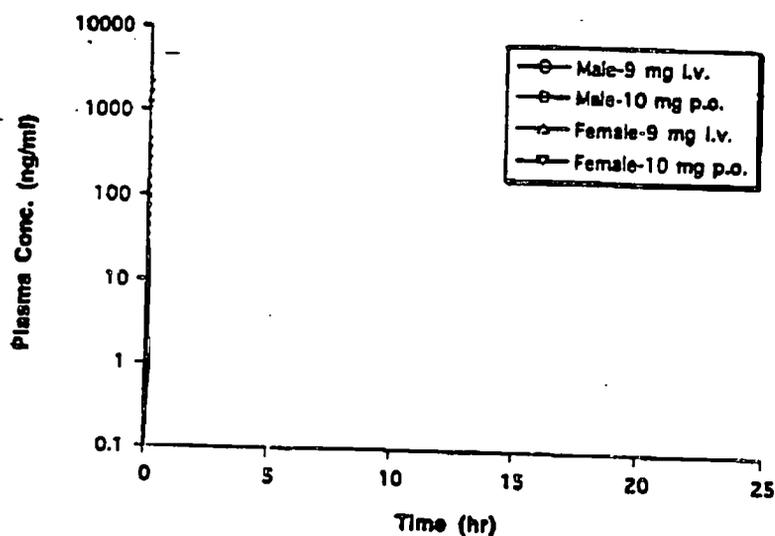
Part I (Males; n=6)	3 mg IV	9 mg IV	18 mg IV	10 mg Oral
$AUC_{0-\infty}$ (ng-hr/ml) ^a	1013 \pm 226	3274 \pm 291	7535 \pm 1283	2405 \pm 482
C_{max} (ng/ml) ^a	568 \pm 91 ^b	1726 \pm 183 ^b	3717 \pm 197 ^b	377 \pm 91
$T_{1/2}$ (hr) ^c	4.41	5.45	5.36	4.94
Part II (Females; n=6)		9 mg IV		10 mg Oral
$AUC_{0-\infty}$ (ng-hr/ml) ^a	—	3298 \pm 1152	—	2103 \pm 1073
C_{max} (ng/ml) ^a		1989 \pm 359 ^b		313 \pm 210
$T_{1/2}$ (hr) ^c		4.52		4.44

^a Geometric mean and back-transformed standard deviation (SD), specified otherwise.

^b For IV doses, concentrations at the end of infusion.

^c Harmonic mean, specified otherwise.

Figure 1: -



2. SINGLE-DOSE PHARMACOKINETICS IN PATIENTS:

There were no adult patients employed in the PK studies for the 10 mg FCT. Single-dose PK of montelukast was investigated in the following two studies for adolescent and pediatric patients with mild to moderate asthma using 2 mg FCT and 10 mg FCT.

The results of the 2-period study # 021 show that when 1x2 mg and 1x10 mg doses were given orally to adolescent patients (12-17 years old) under fasting conditions, the mean plasma profiles were proportional. Further comparisons of the mean PK parameters between the adolescent patients (study # 021) and the healthy adults (study # 026) are shown in **Table 3** in the Dose Proportionality section.

In the 1-period study # 036 (9-14 years old), a dose of 3 x 2 mg was given orally to pediatric patients (BW \leq 45 kg; Part I) and a dose of 1x10 mg was given orally to other pediatric patients (BW >45 kg; Part II) under fasting conditions. Their mean PK parameters are summarized in **Table 4** in the Dose Proportionality section. In **Table 4**, the mean PK parameters obtained from the pediatric patients (Study # 036) and the healthy adults (study # 026) are also compared.

3. MULTIPLE-DOSE PHARMACOKINETICS IN HEALTHY SUBJECTS:

Single- and multiple-dose PK in healthy young volunteers and single-dose PK in elderly volunteers were investigated in study # 045. Please see the detailed study results in Geriatrics section.

4. BIOEQUIVALENCE:

No bioequivalence (BE) studies were conducted.

5. DOSE PROPORTIONALITY:

The first single-dose dose proportionality trial for 1, 2, 10, and 50 mg FCT was investigated in a randomized 4x4 crossover study (study # 026). The above doses were given orally at bedtime to healthy adults under fasting conditions. After the completion of the above 4x4 crossover treatments, three additional phases were carried out subsequently, 1) 1x10 mg FCT was given to 10 volunteers only at bedtime (~10 PM) with snack (one bagel with one ounce of cream cheese and 240 ml of whole milk), 2) 1x10 mg FCT was given to all volunteers in the morning under fasting conditions, and 3) a 50 mg montelukast oral solution was also given to all volunteers at bedtime under fasting conditions.

The results of the above study show that 1) mean plasma levels of montelukast increased proportionality with oral doses 1-10 mg except that the absorption from the 50 mg dose was increased less proportionally, 2) the evening snack slightly increased the mean peak plasma levels (C_{max}) (8% ↑, $p > 0.05$) and AUC (6% ↑, $P > 0.05$), but significantly shortened the mean T_{max} from 4.2 hr to 2.6 hr ($p < 0.05$) [data not shown here], 3) the 10-mg dose when given under fasting conditions at bedtime had slightly lower AUC ($P > 0.05$) but significantly lower C_{max} ($p < 0.05$), larger T_{max} ($p < 0.05$), and shorter $T_{1/2}$ ($p < 0.05$) than those in the morning (the last two rows in Table 3 below), and 4) the relative bioavailability (F_{rel}) of 1x50 mg tablet dose under fasting conditions was estimated to be around 82% as compared to the 50 mg oral solution.

Comparisons of mean PK parameters between adolescents (study # 021) and adults (study # 026) receiving 2 and 10 mg FCT under fasting conditions are summarized below in Table 3:

Table 3:

Subjects	Dose	Dosing Time	N	AUC _{0-∞} (ng-hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	T _{1/2} (hr)
Adolescents (12-17 years old)	2 mg	Morning, Fasting	16	671 ± 173	95.9 ± 28.5	3.5 ± 1.2	4.0
Adults	2 mg	Bedtime, Fasting	16	564 ± 102	76.5 ± 16.5	3.8 ± 1.4	4.3
Adolescents (12-17 years old)	10 mg	Morning, Fasting	16	3224 ± 1097	490. ± 190.	4.1 ± 0.9	4.3
Adults	10 mg	Bedtime, Fasting	16	2647 ± 672	354 ± 93	4.3 ± 1.0	3.9
Adults	10 mg	Morning, Fasting	16	2690. ± 867	421 ± 145	3.0 ± 1.0	5.5

Conclusion (from the above interstudy comparisons):

For either 2 or 10 mg FCT dose, adolescent patients all had higher mean C_{max} and AUC values than healthy adults which could be due to differences in body weight (BW) between adolescents and adults.

Additional comparisons of mean PK parameters between pediatric receiving 3x2 mg FCT (study # 036) and 1x10 mg FCT and adults (study # 026) receiving 1x10 mg FCT under fasting conditions are summarized below in **Table 4**:

Table 4:

Subjects	Dose	Dosing Time	N	AUC _{0-∞} (ng-hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	T _{1/2} (hr)
Pediatrics (10-13 years old)	6 mg	Morning, Fasting	9	2929 ± 994	444 ± 97	4.0 ± 0.7	3.4
Pediatrics (9-13 years old)	10 mg	Morning, Fasting	9	3528 ± 1883	526 ± 413	4.0 ± 0.3	4.2
Adults	10 mg	Bedtime, Fasting	16	2647 ± 672	353 ± 93	4.0 ± 1.0	3.9
Adults	10 mg	Morning, Fasting	16	2690. ± 867	421 ± 145	3.0 ± 1.0	5.3

The above interstudy comparisons show that 1) the 6 mg FCT dose, when given to pediatrics in the morning under fasting conditions, had higher mean C_{max} and AUC as compared to 10 mg dose given to healthy adults in the morning or at bedtime (Row 1 vs. Row 3 or 4 in Table 4) and 2) the 10 mg FCT dose, when given in the morning under fasting conditions to pediatrics, had even higher mean C_{max} and AUC values as compared to those for healthy adults (Row 2 vs. Row 3 or 4 in Table 4).

Conclusion (from the above interstudy comparisons):

For either 6 or 10 mg FCT dose, pediatric patients all had higher mean C_{max} and AUC values than healthy adults. Again, it could be due to differences in BW between pediatrics and adults. Therefore, the above comparisons confirmed that pediatric patients (9-14 years old) should receive a lower dose if comparable mean C_{max} and AUC values (for an adult 10 mg dose) are targeted.

The second single-dose dose proportionality study for 1x2, 1x5, and 1x10 mg CT plus 1x10 mg FCT was conducted in healthy male volunteers under fasting conditions in the morning (a randomized 4x4 crossover trial, Study # 034). The results of the above study show that 1) for 2, 5, and 10 mg CT, plasma levels of montelukast increased proportionality with doses and the mean T_{max} values were similar, around 1.9 to 2 hr, 2) when compared to the 10 mg FCT, the 10 mg CT gave higher mean C_{max} (48% \uparrow , $p < 0.05$) and AUC (20% \uparrow , $p < 0.05$), 3) shorter mean T_{max} (50% \downarrow , $p < 0.05$), and 4) similar mean $T_{1/2}$ values (4.8 vs. 4.6 hr). It was concluded that 10 mg CT had faster and better absorption than 10 mg FCT in adults.

5. FOOD EFFECTS:

The food effect on montelukast PK was investigated in a 5x5 crossover study for both the 10 mg FCT and 5 mg CT given to healthy volunteers in the morning under fasting and fed conditions plus a 7-mg IV dose (study # 060). A high fat meal [2 fried eggs, 2 strips of bacon, toast with two pats of butter, 3 ounces of hash brown potatoes, and one glass (8 ounces) of whole milk] was consumed within 20 min and the above oral doses were taken within 5 min following the meal.

The results show that for the 10 mg FCT given under fasting and fed conditions, 1) the mean F_{abs} values were calculated to be about 64% for both, 2) the mean C_{max} values were similar (422 ± 106 and 401 ± 99 ng/ml; $p > 0.05$), and 3) no significant differences were found in T_{max} (3.0 vs. 3.4 hr; $p > 0.05$).

For the 5 mg CT given under fasting and fed conditions, the results (being normalized to the 10 mg dose) show that 1) the mean F_{abs} value was significantly decreased from 73% (fasting) to 63% (fed; $p < 0.05$), 2) the mean C_{max} value was also significantly decreased from 488 ± 66 (fasting) to 256 ± 82 ng/ml (fed; $p < 0.05$), 3) the mean T_{max} value was increased significantly from 2.3 hr (fasting) to 4.0 hr (fed; $p < 0.05$). It was concluded that food had minimum effects on the 10 mg FCT, but it had significant effects on the 5 mg CT in healthy adults.

6. METABOLISM AND IN VITRO:

The in vivo metabolic pathway and possible metabolites of montelukast in mice, rats, monkeys, and humans were identified as shown below in Scheme 1:

Following IV or oral administration of ^{14}C -montelukast to rats and mice, the acylglucuronide conjugate (M1), predominated in the bile while sulfoxide metabolite (M2), the 21- and 36-hydroxylated analogs (M5 and M6, respectively), a phenolic derivative (M3), and the dicarboxylic acid (M4) were relatively minor metabolites in bile. Post IV dosing, 1) 82.4% of radioactivity was excreted in feces while only 0.7% was excreted in urine in 4 days, 2) only 4% of radioactivity was accounted for as the parent drug in the bile, and 3) enterohepatic recirculation of the drug in rats was not significant. Similar results were obtained in monkeys, 88% in feces and 0.3% in urine 4 days post dosing.

Some basic PK parameters for montelukast obtained from animals and humans previously are summarized below in Table 5:

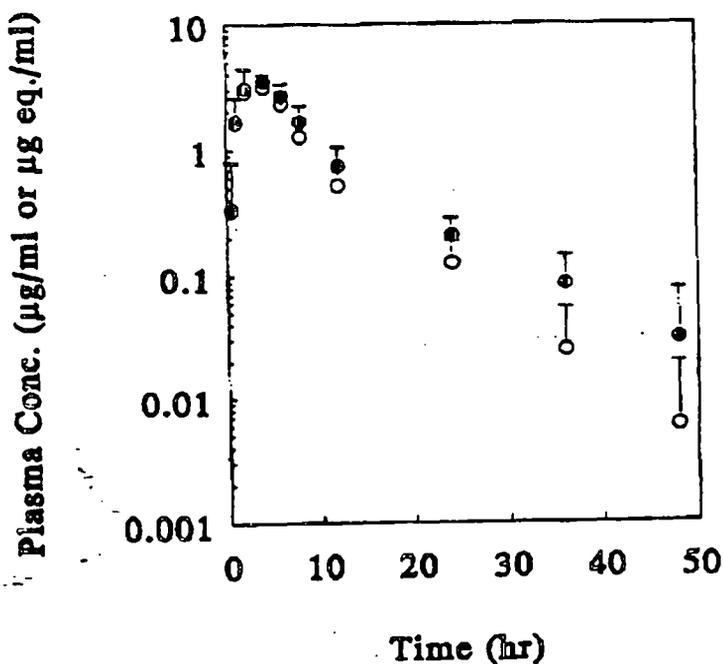
Table 5:

Species	Plasma Clearance (mL/min/kg)	Half-Life (min)	V_{dss} (L/kg)	Oral Bioavailability (% of Dose)	Protein Binding (% Bound)
Rat	15	90	0.7	33	99.7
Mouse	11	75	0.8	50	99.1
Monkey	2.5	125	0.2	47	99.6
Human	0.6	300	0.15	67	99.6

The mean blood/plasma ratio in human was calculated to be 0.65 and albumin was the main component responsible for protein binding in plasma.

Oral administration of 100 mg ^{14}C -montelukast (in capsules) to healthy volunteers was investigated in Study # 023. The mean plasma drug profiles are shown below in Figure 2:

Figure 2:



The results of study # 023 show that 1) montelukast (o) predominated in plasma [$>80\%$ of total radioactivity (•)], 2) the biliary excretion of

montelukast and its metabolites is a major route of elimination ($86.3 \pm 3.7\%$ in feces 5 days postdosing) while the renal excretion is insignificant ($<0.2\%$), and **3)** the mean T_{max} and $T_{1/2}$ obtained for montelukast are consistent with those reported previously. However, no detailed information on the % of each metabolite (M1 to M6) found in the feces was presented in this study.

Biliary excretion of 50 mg ^{14}C -montelukast was further investigated in healthy volunteers (Study # 051). After oral administration of ^{14}C -montelukast (in capsules), bile along with duodenal juice was collected through an oro-gastroduodenal tube between 2 and 8 hr and blood samples were collected up to 10 hr postdosing (under fasting conditions; Part I). For Part II, after an overnight fast, a defined fatty meal was given 5 hr prior to the same dose. Bile and duodenal juice was similarly collected between 8 and 12 hr and blood samples up to 10 hr postdosing. In all subjects, cholecystokinin C-terminal octapeptide (CCK-8) was administered IV 2 hr prior to the end of biliary collection to enhance bile flow and facilitate collection.

The results of Study # 051 show that **1)** the % of radiolabeled dose recovered in the bile ranged from 5.65 to 19.65 % (2-8 hr; Part I) and in Part II, it was 3.09 to 11.00% (8-12 hr), **2)** montelukast was also extensively metabolized in humans, **3)** M4 predominated in bile, but it was not found in plasma, **4)** M3, M6, and M5 (in order of amounts) and trace amounts of M1 and M2 were found in the bile, **5)** montelukast accounted for nearly ($>98\%$) all the radioactivity in plasma over the initial 10 hr postdosing, and **6)** only around 2% of radioactivity in plasma was identified as M5 and M6 (concentrations were at least 10 times lower than montelukast) and no other metabolites were seen.

The results of in vitro studies using animal and human (adult and pediatric) liver microsomes show that **1)** ketoconazole (a 3A4 inhibitor) strongly inhibited the formation of M5 and M2, **2)** sulfaphenazole (a 2C9 inhibitor) strongly inhibited the formation of M6, **3)** other inhibitors for 1A2, 2A6, 2C19, and 2D6 had little effects on the metabolism of montelukast, and **4)** no significant differences in the results obtained from adult or pediatric liver microsomes.

On the other hand, montelukast **1)** strongly and competitively inhibited methyl hydroxylation of tolbutamide (a 2C9 marker), **2)** to a much lesser extent, inhibited 6β -hydroxylation of testosterone (a 3A marker) and 4'-hydroxylation of S-mephenytoin (a 2C19 marker), and **3)** had little effects

on other markers' activities, i.e., phenacetin (a 1A2 marker), coumarin (a 2A6 marker), and debrisoquine (a 2D6 marker) in vitro.

The above results are also confirmed by further in vitro investigations that human recombinant CYP3A4 formed M2 and M5 but not M6 and recombinant CYP2C9 formed M6 but had little effects on M2 and M5 formation. It should be noted that 1) M2, M5, M6 or M4 had stereoisomers (e.g., M2a/b, etc. as shown in **Scheme 1**, since the formation of sulfoxide at S or the hydroxylation at C21, or C36 position would create a second chiral center.

Finally, from the in vitro pharmacological study, it is reported that M6 binds to the CysLT₁ receptor nearly as avidly as the parent drug, while M5 binds 8- to 10-fold less. Since the plasma levels of M5 and M6 are at least 10 times lower than montelukast, the overall contribution of metabolites to montelukast PK and/or pharmacologic effects is seemingly less of a concern.

7. PEDIATRIC POPULATION:

Single-dose PK in pediatric patients (9-14 years old) has been studied previously in study # 036 using 2 and 10 mg FCT. In another study # 039, additional single- and multiple-dose PK were investigated in pediatric patients (6-8 years old) who received 1x5 mg CT in the morning for Day 1 in a single-blind phase. The same drug was given daily in the morning to only 14 pediatric patients (Part I) up to Day 15 in a double-blind phase. For rest of 5 (Part II) received placebo from Day 2 through Day 15. Complete PK data/information (Day 1) were obtained from all the pediatric patients. Trough plasma levels (prior to next dosing at bedtime) for Days 2, 8 and 15 (last dose) and plasma levels at expected T_{max} (2 hr postdosing) for Day 8 and 15 were obtained from Part I. Mean PK parameters (Day 1) obtained from the above study # 039 are summarized below in **Table 6**:

Table 6: Single-Dose PK (Day 1)

Subjects	Dose	Dosing Time	N	AUC _{0-∞} (ng-hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	T _{1/2} (hr)
Pediatrics (6-8 years old)	5 mg CT	Morning, Fasting	19	2928 ± 904	495 ± 129	2.0 ± 1.3	3.7

The above study results show that 1) for Day 1, pediatric patients had comparable mean C_{max} and AUC values as compared to adolescent patients who received a single dose of 3x2 mg FCT, but had higher mean C_{max} and AUC values than those in healthy adults who received a single

10-mg FCT dose (Table 4), 2) trough plasma levels were found to be 9.0 ± 7.2 ng/ml (Day 2, 0 hr), 5.9 ± 5.1 ng/ml (Day 5, 0 hr), and 10.8 ± 10.3 ng/ml (Day 15, 0 hr) and they were reportedly not significantly different ($p > 0.05$), and 3) mean plasma levels at 2 hr postdose (expected C_{max}) for Day 1 (n=19), Day 8 (n=10) and Day 15 (n=10) were found to be 472 ± 158 ng/ml, 325 ± 170 ng/ml and 332 ± 205 ng/ml, respectively ($p > 0.05$). Finally, further examination of plasma specimens obtained at steady state from these young children receiving 5 mg CT QD or from young adults receiving 10 mg FCT QD show that 1) montelukast metabolites were below detection limits and 2) seemingly the accumulation of metabolites in the body did not occur.

8. HEPATIC IMPAIRMENT:

Montelukast oral PK in adult subjects with mild (n=4) to moderate (n=4) hepatic insufficiency (Child-Pugh's scale 5 to 6 and 7 to 9, respectively) was investigated in a 2x2 crossover study # 057 under fasting conditions. A 10 mg FCT and a 7-mg IV solution were given. The results show that 1) for the 10 mg oral dose, the mean C_{max} , T_{max} , and AUC values were 313 ± 240 ng/ml, 4.0 ± 2.1 hr, and 3167 ± 1300 ng-hr/ml, respectively, 2) their mean F_{abs} , CL, $Vd_{0.5}$, $T_{1/2}$ values (after IV) were 52%, 27.4 ± 7.8 ml/min, 13.4 ± 5.1 liters, and 7.4 ± 1.9 hr, respectively, and 3) the overall elimination of montelukast in these subjects was somewhat impaired when compared to the healthy young volunteers. The PK of montelukast in severe hepatic insufficiency, however, was not studied.

9. RENAL IMPAIRMENT:

It was reported by the sponsor that since 1) montelukast was extensively metabolized and 2) the metabolites were mainly biliary excreted and <0.2% of an oral dose was excreted in urine as metabolites, no PK studies in renally impaired patients were conducted. The sponsor's justification is seemingly reasonable.

10. GENDER:

Montelukast PK in both male and female volunteers were investigated previously in study # 033 and no major gender differences were found.

11. GERIATRICS:

Study # 045 consisted of 1) an open-label, single- and multiple-dose PK study in healthy young adults (means of 31 years old and 67 kg) who

received 1x10 mg FCT (Part I) and 2) a 2x2 crossover single-dose PK study for investigating oral bioavailability of 1x10 mg FCT as compared with a 7-mg-IV dose in healthy elderly volunteers (means of 70 years old and 72 kg; Part II). The results of study # 045 (normalized to the 10 mg dose) are summarized below in Table 7:

Table 7: (Normalized to the 10 mg Dose)

Subjects	Dosing Time	N	AUC _{0-∞} (ng-hr/ml)	AUC ₀₋₂₄ (ng-hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	T _{1/2} (hr)
Elderly (IV)	Morning, Fasting	12	5620. ± 1685	-----	-----	-----	6.7
Elderly (Oral)	Morning, Fasting	12	3323 ± 1345	-----	495 ± 190.	2.8 ± 1.0	6.6
Young (Day 1, Oral)	Morning, Fasting	12	3624 ± 1258	3504 ± 1198	542 ± 173	3.0 ± 1.0	5.3
Young (Day 7, Oral)	Morning, Fasting	12	-----	3978 ± 1317	603 ± 137	2.7 ± 1.0	5.6

The results of Study # 045 show that for healthy elderly subjects, 1) their mean F_{abs} was estimated to be around 61%, 2) the mean trough plasma levels between Days 3 and 7 were 20.3, 20.1, 18.4, 19.8, and 24.2 ng/ml, 3) the mean plasma CL was 30.8 ± 8.6 ml/min which was lower (p<0.05) than that for healthy young volunteers, 4) they had similar mean single-dose AUC and C_{max} values (p>0.05) as compared to healthy young adults, and 5) mean T_{1/2} averaged 6.6 hr which was significantly longer than that for healthy young volunteers (5.3 hr; p<0.05). The results further show that for healthy young adults, montelukast accumulates slightly but significantly [~14%; in terms of mean AUC₀₋₂₄ value (p<0.05)] at steady state after QD dosing for 7 days.

12. DRUG-DRUG INTERACTIONS:

Six pivotal plus 2 supportive drug-drug (D-D) interaction studies were submitted. Healthy male and/or female volunteers were employed in these D-D studies. Most of the pivotal D-D studies investigated the effects of multiple doses of montelukast on the PK of several drugs, e.g., theophylline, prednisone and prednisolone, oral contraceptives, digoxin, terfenadine, and warfarin, while only one study investigated the effects of multiple doses of phenobarbital on montelukast PK.

1. Theophylline:

In a randomized, double-blind, placebo-controlled, 2x2 crossover study (# 047), 1x 10_mg FCT was given QD for 11 days. On day 10, a single IV dose of theophylline (4.65 mg/kg) was given by a 20-min infusion. On Days 10 and 11, blood samples were taken at time zero (end of infusion) up to 30 hr after completing the infusion. A 2-week washout period was used between treatment phases.

The results of study # 047 show that when compared the montelukast group to the placebo group, 1) theophylline AUC was slightly decreased (112 vs. 121 mg-hr/L; $p < 0.05$) and CL was slightly increased ($p < 0.05$) and 2) the mean concentrations at the end of infusion were comparable (14.1 vs. 13.5 mg/L; $p > 0.05$). It is concluded that the therapeutic dose of montelukast did not have clinically meaningful effects on theophylline.

In the 2 earlier D-D studies for theophylline (both in 10 healthy male volunteers), higher doses of montelukast were given, i.e., 1) 200 mg QD for 6 weeks and 250 mg of theophylline was given orally before and after montelukast administration (supportive Study # 012) or 2) 200 mg TID was given for more than 8 days and theophylline 250 mg was given orally on Day 8 (supportive Study # 008). As the montelukast doses increased (from 200 mg QD in Study #012 to 200 mg TID in Study #008), theophylline's mean AUC values were decreased gradually and significantly (30%↓ and 66%↓, respectively; both $p < 0.05$) and mean $T_{1/2}$ values were decreased as well (from 8.7 hr to 4.7 and 3.7 hr, respectively; $p < 0.05$).

2. Prednisone and Prednisolone:

In the same study # 012, the plasma levels of prednisone (oral 20 mg) and prednisolone (IV 20 mg) before and after montelukast administration (200 mg QD x 6 weeks) were monitored in separate and parallel subgroups. The results show that 1) for prednisone, only the mean AUC value was decreased significantly (29%↓; $p < 0.05$) and 2) for prednisolone, no significant changes were found.

3. Oral Contraceptive:

In a randomized, double-blind, 2x2 crossover study # 018, female volunteers received Ortho-Novum 1/35 (35 µg EE and 1 mg NET) during each of the two treatment phases. On Day 1, 2, 3, or 4 on the menstrual cycle and on Novum treatment, subjects also received 100 mg montelukast in capsules or matched placebo QD for 8 days. On Day 8 of each treatment phase, subjects' oral contraceptive components (EE and

NET) in serum were monitored. There was a washout period of 14-20 days. The results show that no significant changes in the mean plasma profiles between treatment phases were found nor were in mean C_{max} or AUC values for EE ($p > 0.05$) and for NET ($p > 0.05$). In addition, sex hormone binding protein levels were also monitored on Days 1 and 8. No significant differences ($p > 0.05$) were found between treatments on either Day 1 or Day 8.

4. Digoxin:

In a randomized, double-blind, placebo-controlled, 2x2 crossover study # 053, either 1 x 10 mg montelukast FCT or matched placebo was given QD to healthy volunteers for 11 days. A single oral dose of digoxin (0.5 mg) was given on Day 7 of both phases. A washout period of 14 to 21 days was used. Plasma immunoactive digoxin levels were monitored on Day 7 at predose (time zero) and up to 120 hr postdosing. Immunoactive digoxin in urine was also monitored at certain intervals up to 120 hr.

The results show that no significant differences for either mean C_{max} or $AUC_{0-\infty}$ values ($p > 0.05$) between Mon+Dig and Pbo+Dig. It was true for the mean T_{max} , $T_{1/2}$, or cumulative (120-hr) urinary immunoactive digoxin excretion ($p > 0.05$).

5. Warfarin:

In a randomized, double-blind, placebo-controlled, 2x2 crossover study # 055, either 1x 10 mg montelukast FCT or matched placebo was given QD to healthy volunteers for 12 days. A single oral dose of warfarin (30 mg) was given on Day 7 of both phases. A washout period of 14 to 21 days was used. Both plasma R(+) and S(-) warfarin levels were monitored for 144 hr postdosing of warfarin. The international normalized ratio (INR) was also calculated.

The results show that no significant differences in PK of R(+) or S(-) warfarin were found. For warfarin plasma levels, the GMR (geometric mean ratios) of AUC_{0-144} between Mon/W vs. Pbo/W is 0.96 for R(+) warfarin ($p > 0.05$) and that for S(-) warfarin is 1.00 ($p > 0.05$). It is also true that the GMR of C_{max} is 0.96 ($p > 0.05$) for R(+) warfarin and that for S(-) warfarin is 1.00 ($p > 0.05$). For INR (2.21 vs. 2.24), the GMR is 0.99 ($p > 0.05$) and that for INR AUC_{0-144} is 0.99 ($p > 0.05$).

6. Terfenadine:

In a randomized, placebo-controlled, 2x2 crossover study # 048, subjects received terfenadine 60 mg BID for 14 days in both phases. Montelukast, 1x 10 mg FCT, or matched placebo was given QD on Days 8 through 14

(7 days). At least a 2-week washout period was used. Plasma levels of terfenadine and its metabolite (carboxyterfenadine) were monitored on Day 14. The QTc intervals were also monitored at baseline (Day 1) and on Days 7 and 14.

The results of the study show that on Day 14, montelukast did not change the plasma profiles or mean AUC and C_{max} for terfenadine (p>0.05) or carboxyterfenadine (p>0.05) as shown below in **Table 8**:

Table 8: (On Day 14)

Carboxyterfenadine	N	AUC₀₋₁₂ (ng-hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	T_{1/2} (hr)
Mon/T	13	1659 ± 548	248 ± 99	2.7 ± 1.3	13.1
Pbo/T	13	1705 ± 381	260. ± 80.	2.3 ± 0.8	12.0
Terfenadine		AUC₀₋₁₂ (pg-hr/ml)	C_{max} (pg/ml)		
Mon/T	13	9627 ± 6276	1833 ± 1116	1.0 ± 0.5	19.3
Pbo/T	13	9635 ± 5560.	1692 ± 899	0.8 ± 0.2	18.8

The maximum QTc intervals observed were not prolonged and no significant differences were found for GMR between Days 14 and 7 for Mon\T (ratio 1.00, p>0.05), or for Pbo\T (ratio 1.00, P>0.05). It is also true for Mon\Pbo (ratio 0.99, p>0.05).

7. Phenobarbital:

In a placebo-controlled, fixed-sequence, 2-period study # 058, 1) a single dose of 1x 10 mg montelukast FCT was given alone to all the volunteers in the morning (Period 1) and 2) either 100 mg phenobarbital (n=10) or placebo (n=4) was given orally at bedtime for 14 days, and 3) another single dose of 1x 10 mg montelukast was given concomitantly on Day 14 (Period 2). For each period, plasma levels of montelukast were monitored in 10 subjects who participated in both Periods 1 and 2.

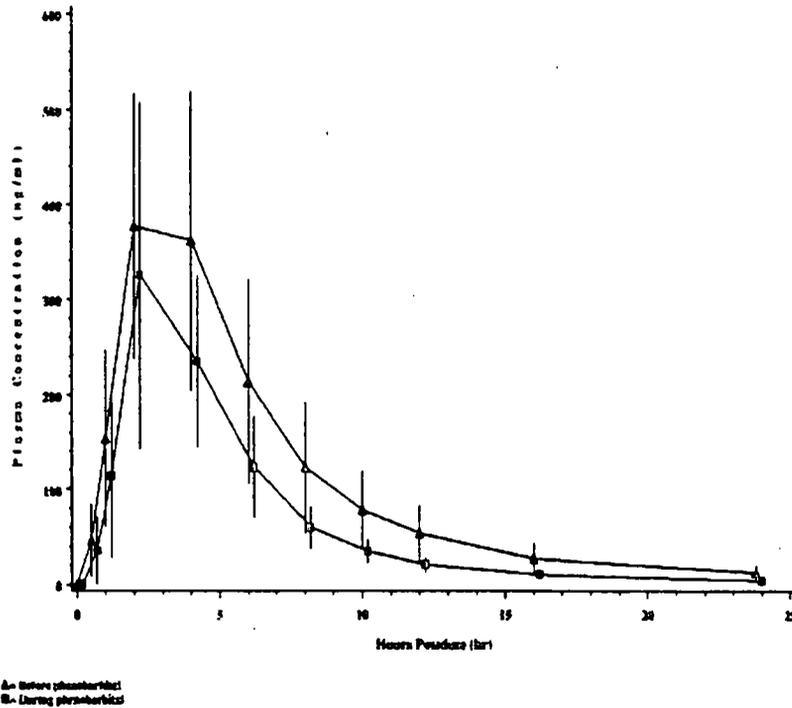
The results show that phenobarbital, which is known to be a CYP 3A4 inducer did cause decreases in montelukast mean AUC (38%↓; p<0.05), and T_{1/2} (22%↓; p<0.05) values except mean C_{max} (20%↓; p>0.05) and T_{max} (p>0.05) values. Therefore, phenobarbital was concluded to have significant effects on montelukast PK through CYP3A4 induction. The mean PK data (n=10) and mean plasma profiles are shown in **Table 9** and **Figure 3** below:

Table 9: Montelukast PK

Treatments	AUC _{0-∞} (ng-hr/ml)	C _{max} (ng/ml)	T _{max} (hr)	T _{1/2} (hr)
Before Phenobarbital	2466 ± 1333	380. ± 163	2.0 ± 1.0	3.6
After Phenobarbital	1541 ± 704	304 ± 199	2.0 ± 0.8	2.8

Figure 3:

Mean (± SD) Plasma Concentrations of Montelukast When Administered During and Before Phenobarbital 100 mg Daily for 14 Days (N = 10)



13. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

The PK and PD relationship of montelukast was examined previously in several clinical studies using subgroups of adult patients (provided as references in Item 6). Dosing regimen of 10 mg QD and higher QD or BID doses were investigated. The preliminary results obtained from the LTD₄ challenge studies (# 005 and 011) show that the minimum effective montelukast plasma level could be as low as 120 ng/ml.

Results obtained from Study #013 show that 1) the mean maximal % decrease in FEV₁ (forced expiratory volume in one second) after exercise was 29.6% after placebo, 17.1% after a 50 mg BID regimen, and 14.0% after a 100 mg QD regimen and 2) both treatments were significantly

different from the placebo ($p < 0.05$), but no differences between the treatments were found. In Study #009, efficacy endpoints (including morning FEV₁, 12 hr postdosing, daytime asthma symptom scores, patient-reported β -agonist use, and morning peak expiratory flow rates as well as a composite score combining the scoring for each of these key points) were reviewed and patients' morning (\approx 12 hr postdosing) plasma montelukast levels were monitored for 10, 100, or 200 mg QD dosing regimen (given at bedtime) and also for 10 or 50 mg BID dosing regimen. The results are summarized below in **Table 10**:

Table 10:

Treatment	Total N	Composite Score of Rank Sum	PK Subgroup N	Plasma Montelukast Level (ng/ml)
Placebo	58	517 (\pm 238) ^a	-----	-----
10 mg QD	57	725 (\pm 274) [*]	15	140 (\pm 90) ^a
10 mg BID	54	688 (\pm 298) [*]	10	200 (\pm 140)
50 mg BID	57	708 (\pm 265) [*]	15	440 (\pm 380)
100 mg QD	56	759 (\pm 283) [*]	20	320 (\pm 240)
200 mg QD	61	705 (\pm 316) [*]	14	690 (\pm 650)

^a Mean (\pm SD).

^{*} Significantly different from placebo ($p < 0.05$).

The above results show that 1) dose levels greater than 10 mg QD all had statistically significant effects as compared to placebo and 2) no correlation of efficacy endpoints and plasma drug levels were found. Since the PD responses in these studies were generally maximal ($p > 0.05$) at doses of 10 mg or higher, the sponsor precluded a complete characterization of the PK/PD relationship.

14. FORMULATIONS:

The 10-mg FCT used in most of the pivotal PK studies and in all of the clinical trials for adults was formulation No. HT. It is compositionally and proportionally the same as the to-be-marketed 10-mg FCT in terms of tablet core and it only differs slightly in film coating material as shown below in **Table 11**:

Table 11:

10-mg FCT	<u>To-be-marketed</u>	<u>Clinical Used</u>
Ingredient (mg)		Formulation No.
<u>Tablet Core</u>		(HT)
Montelukast sodium	10.4	10.4
Hydroxypropyl Cellulose NF		
Microcrystalline Cellulose NF		
Lactose Monohydrate NF		
Croscarmellose Sodium NF		
Magnesium Stearate NF		

Tablet core weight (mg)

Film Coating

Hydroxypropyl Cellulose NF
Hydroxypropyl Methylcellulose USP
Titanium Dioxide USP
Red Ferric Oxide NF
Yellow Ferric Oxide NF
Carnauba Wax NF

Total film-coated tablet weight (mg)

The 5-mg CT used in pediatric PK and clinical studies were formulation Nos. CCT and BCT. They are compositionally the same as the to-be-marketed 5-mg CT except slight differences in the amounts of mannitol and/or magnesium stearate as shown below in **Table 12**:

Table 12:

5-mg CT	<u>To-be-marketed</u>	<u>Clinical Used</u>	
Ingredient (mg)		Formulation No.	
<u>Tablet Core</u>		(CCT)	(BCT)
Montelukast sodium	5.2	5.2	5.2
Mannitol USP			
Hydroxypropyl Cellulose NF			
Microcrystalline Cellulose NF			
Red Ferric Oxide NF			
Croscarmellose Sodium NF			
Cherry flavor			

Aspartame-NF

Magnesium Stearate NF

Total tablet weight (mg)

The 10 mg FCT and 5 mg CT were manufactured by the final process at West Point, PA. A representative scale for most of the tablet batches was used in most of the PK studies and in the Phase IIa and III clinical trials. However, the commercial batches of 10 mg FCT and 5 mg CT are to be made at facilities in Wilson, NC.

15. DISSOLUTION METHODOLOGY AND SPECIFICATION:

A pre-NDA meeting was held in January, 97 between the sponsor and the Agency for an alternative methodology (Method 2). Additional dissolution data for comparing Methods 1 and 2 were provided in a bridging study using bio- and clinical batches:

Since Method 2 is the best one the sponsor could come up with at this moment, it was agreed at the end of the meeting that Method 2 as shown below would be used for both the 10 mg FCT and 5 mg CF on an interim basis:

As agreed upon in the above industry meeting, the sponsor submitted dissolution and 3-month stability data using Method 2 for the 10 mg FCT and the 5 mg CT (one commercial batch each) that were made in Wilson, NC.

The dissolution Method B is thus not discriminatory.

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III. GENERAL COMMENTS (Nos. 7 to 10 need to be sent to the sponsor)

1. The clinical sites of two pivotal studies (Study # 034 and # 039) were requested for audit by OCPB as soon as the NDAs were filed. Study # 034 was conducted in healthy adults which provided a link between the 10 mg FCT and 5 mg CT and Study #039 employed pediatric patient 6 to 8 years old for the 5 mg CT. Since Study # 034 was conducted in Netherlands, only Study # 039 (conducted in the US) was audited in June of 1997.

The results of the above audit (submitted to OCPB on 08/12/97) show that the study (# 034) is overall acceptable and no Form 483 was issued. However, several minor deficiencies were identified. On 10/02/97, the sponsor responded to those deficiencies and agreed to comply with the Agency's regulations/recommendations. The sponsor's responses are acceptable.

2. In most of the PK/Bio studies conducted, the individual AUC value was calculated using a computer program instead of traditional trapezoidal rule. Comparisons of the results obtained from the above methods were therefore requested. The results were submitted by the sponsor and a statement of justification was also provided.

It was concluded that 1) less than 4% difference in individual AUC value and 2) less than 2% in the mean AUC value using the above methods were found. Therefore, the AUC calculation using the program is acceptable.

3. In most of the PK/Bio studies conducted, the PK parameters were normalized to potency, e.g., a factor of 9.93 was used in Study # 033 for the 10 mg FCT. As reported by the sponsor that the mean value (9.93) was the assay averaged drug content. However, the following information

was not provided, 1) the mean value of 9.93 being obtained from one batch or several batches, 2) no. of tablets used, and 3) the SD of the mean. The above comment was already conveyed to the sponsor in a telecon on 11/20/97 and the sponsor submitted their responses on 11/26/97 and their are found acceptable.

4. As agreed upon in the meeting between the Agency and Merck, dissolution Method 2

was selected on an interim basis. Since the site of manufacture is to be changed from West Point, PA. to Wilson, NC., additional dissolution information using Method 2 for the 10 mg FCT and 5 mg CT (one commercial batch each) that were to be manufactured in the new site, Wilson, NC was, therefore, requested in the meeting. However, submitted were only the means without SD or no. of tablets used. The above information was also requested in the 11/20/97 telecon and the sponsor submitted their responses on 11/26/97 and their are found acceptable.

5. No BE studies were conducted in these NDAs. Since the formulation changes between the clinically tested and the to-be-marketed tablets (for both 10 mg FCT and 5 mg CT) were minor and they were all within the Level 1 acceptable limits as stated in the SUPAC. No BE studies are needed.
6. There were no studies conducted for the PK of 5 mg CT given in the evening nor with food or snack in healthy adults or pediatric patients. Adult PK studies showed little differences in PK parameters between AM and PM dosing under fasting conditions, so likelihood of a time-related difference in children's AM and PM PK is small.

In the absence of data on the effect of food on pediatric PK parameters, the effects of food in children must be extrapolated from adult study using the 5 mg CT that showed significant changes in F_{abs} , C_{max} , and T_{max} . It should therefore be presumed that children receiving the 5 mg CT at bedtime will likely have lower F_{abs} and C_{max} and an increase T_{max} relative to pediatric PK trials which were conducted under fasting conditions.

7. Study # 045 had much higher mean AUC (45%↑) and C_{max} (43%↑) for a 10 mg FCT dose (given under fasting conditions) as compared to the overall means obtained from other studies (# 033, 026, 034, 060, and 058). The same assay method B was reportedly employed in the above studies. Therefore, it is recommended that the above studies be reviewed and a rationale be provided to the Agency for the above discrepancies.

conducted in early studies using doses which exceeded the dose to be recommended in the PI.

Additionally, blood/plasma ratio, protein binding, pharmacologic activity for possible metabolites, identification of the enzyme(s) responsible for the metabolism of this drug using liver microsomes, enzyme markers and inhibitors, etc. were investigated in vitro and are reviewed. Finally, the 5 supportive PK studies are briefly reviewed as well.

RECOMMENDATION:

NDA 20-829 (montelukast sodium 10 mg FCT for adults) and NDA 20-830 (montelukast sodium 5 mg CT for children 6-14 years old) that were filed by Merck Research Labs on 02/24/97 have been reviewed by the Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the information submitted to the human PK/Bio section is acceptable from the CPB perspective. There are general comments and a labeling comment provided in pages 24-26. Finally, General Comment Nos. 7 to 10 and the Labeling Comment need to be conveyed to the sponsor ASAP.

CPB Briefing on 12/09/97:

Drs. P. Honig (MO), D. Conner, L. Lesko, S.M. Huang, J. Balain, M.L. Chen, J. Lazor, R. Miller, E. Fadiran, and R. Yuan and Mr. J. Hunt

ISI
11/26/97

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Dale P. Conner, Pharm.D.

DPC 12/01/97

FT initialed by Dale P. Conner, Pharm.D.

ISI 1/8/98

cc: NDAs 20-829 and 20-830, HFD-570 (Honig and Trontell, Kuzmik), HFD-870 (M.L. Chen, T.M. Chen), HFD-650 (D. Conner), CDR (B. Murphy).

**NDA 20-829 (Montelukast 10 mg Film-Coated Tablets)
and NDA 20-830 (Montelukast 5 mg Chewable Tablets)**

Appendix 1

Proposed Package Insert (11/07/97 Version)

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3 pages