

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-475**

**MEDICAL REVIEW(S)**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** April 14, 2003

**FROM:** Paul J. Andreason, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approval of Methylin® Chewable Tablets

**TO:** File, NDA 21-475  
[Note: This memo should be filed with the sponsor's February 14, 2003 "Response to Approvable" submission.]

**1.0 BACKGROUND**

Methylin® Chewable Tablets are a chewable formulation of methylphenidate. Mallinkrodt received an Approvable Action Letter from the Division on October 18, 2002. The Approvable Action outlined Chemistry and Biopharmaceutics (OCPB) requirements and draft labeling changes. There were no Clinical Review deficiencies that needed to be addressed.

**2.0 CHEMISTRY**

The sponsor addressed all of the Chemistry Review deficiencies including adding information to labeling on aspartame — and guar gum choking risks. These were discovered as deficiencies by the Chemistry Review Team during the review of the Response to Approvable submission.

**3.0 PHARMACOLOGY**

Since methylphenidate is a marketed drug substance and the ingredients are known from other products, there were no pharmacology/toxicology issues to consider in this submission.

**4.0 BIOPHARMACEUTICS**

The sponsor accepted all of draft labeling changes suggested by OCPB.

**5.0 CLINICAL**

There were no outstanding clinical deficiencies that needed to be addressed in this submission.

**6.0 RECOMMENDATIONS AND CONCLUSION**

From a clinical standpoint, I recommend that the Division issue and Approval Action Letter. The sponsor appears to have addressed all other outstanding deficiencies. Final draft labeling is attached to the draft Approval Action Letter.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** October 16, 2002

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for approvable action for an NDA for Methylin CT, a chewable tablet formulation of methylphenidate (in 2.5, 5, and 10 mg strengths), for ADHD and narcolepsy.

**TO:** NDA 21-475 for Methylin CT  
[Note: This memo should be filed with the 12-19-01 original submission of this NDA.]

This is a 505(b)(2) application for a chewable tablet formulation of methylphenidate (in 2.5, 5, and 10 mg strengths). Methylphenidate is currently approved for the treatment of ADHD and narcolepsy, and is available in several different immediate release and modified release formulations. However, this would be the first chewable tablet formulation. The rationale for this form is to "provide additional flexibility in dose titration as well as ease of dosing for those patients having difficulty swallowing solid oral dosage forms."

The application included CMC information and the results of three bioequivalence trials comparing Methylin CT with Ritalin, the reference product.

CMC: The CMC information has been reviewed by Xiao-Hong Chen, Ph.D., from the chemistry group. CMC has concluded that this NDA is approvable, however, they have identified several deficiencies that need to be addressed prior to final approval.

DMETS has objected to the proposed name.

\_\_\_\_\_ They also have  
some comments regarding container labels.

Pharmacology/Toxicology: There was no need for a pharmacology/toxicology review of this application.

Biopharmaceutics: The results of the bioequivalence trials have been reviewed by Wen-Hwei Chou, Ph.D, from OCPB. The three trials were as follows:

-596: 3-way crossover, fasted, comparing Methylin CT chewed, Methylin CT swallowed whole, and Ritalin.

-610: 3-way crossover, fasted, comparing Methylin CT chewed, Methylin AQ (an aqueous form being reviewed under a separate NDA), and Ritalin.

-721: 3-way crossover, comparing Methylin CT (chewed, fed), Methylin CT (chewed, fasted), and Ritalin (swallowed whole, fed).

These BE studies were conducted with the 10 mg strength, and the sponsor requested a biowaiver for the two lower strengths. OCPB has concluded that bioequivalence of the 10 mg Methylin CT tablet to Ritalin 10 mg has been established, and they are willing to grant the biowaiver, based on proportional composition and comparable dissolution profiles. OCPB has concluded that this NDA is approvable, however, they have recommended a change in the dissolution specifications and an update of labeling with currently accepted pharmacokinetic language for methylphenidate labeling. We had asked for this update after the filing meeting, but the sponsor has not responded to this request.

Clinical: The clinical data in this NDA were reviewed by Earl Hearst, M.D., from the clinical group. Approximately 95 normal adults were exposed to Methylin CT in the three PK studies conducted as part of the development program for this product. No serious or unexpected adverse events were observed.

Pediatric Rule: The sponsor has requested that we defer the requirement for studies in children under 6, under the Pediatric Rule. However, our current DNDP policy on studies in children under 6 is to not issue written requests for such studies, given that there remains uncertainty about (1) the diagnosis of ADHD in this younger population, (2) how to reliably make the diagnosis, even if it could be considered a legitimate entity, and (3) how to assess patients with this condition, and otherwise efficiently conduct these studies. Given that we are denying PPSRs for such studies, I think we should be waiving such studies, and not deferring them. In fact, a large NIMH study of methylphenidate in ADHD (PATS) is just getting underway. If this study is successful in demonstrating the legitimacy and feasibility of conducting such studies, and demonstrates a treatment benefit, it would be possible, in my view, to extrapolate from the results of this study to all other methylphenidate formulations, making the conduct of any additional studies unnecessary. Thus, I recommend a waiver of this requirement at this time.

Labeling: The proposed labeling is the same as Ritalin labeling, except for changes pertinent to the new formulation. As noted, we will ask for an update of the labeling with regard to pharmacokinetic information. The letter includes the exact language that should be incorporated.

Conclusion: I agree that this application is approvable, and the letter should include our recommended changes to the label, in anticipation of final approval.

APPEARS THIS WAY  
ON ORIGINAL

cc:  
Orig NDA 21,475  
HFD-120/DivFile  
HFD-120/TLaughren/RKatz/EHearst/AHomonnay

DOC: NDA21475.01

APPEARS THIS WAY  
ON ORIGINAL



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

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Thomas Laughren  
10/16/02 03:12:19 PM  
MEDICAL OFFICER

## REVIEW AND EVALUATION OF CLINICAL DATA

**NDA:** 21-475  
**DRUG:** Methylin CT Chewable  
**SPONSOR:** Mallinckrodt  
**MATERIAL SUBMITTED:** NDA for 505(b)(2)  
**SUBMISSION DATE:** 12/19/2001; 01/16/2002; 04/10/2002 (Response to FDA request on dissolution issues), 04/18/2002 (electronic submission)

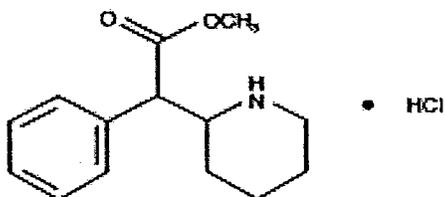
### I. Summary

Methylin® CT (Methylphenidate Hydrochloride Chewable Tablets in 2.5 mg, 5 mg and 10 mg strengths) is an alternate dosage form of Methylphenidate Hydrochloride. It is bioequivalent to Ritalin® Hydrochloride Tablets, the RLD for this 505(b)(2) NDA. Methylin CT (methylphenidate hydrochloride chewable) was submitted as a 505(b)(2) NDA with the proposal to rely primary on the labeling, application and previous marketing experience of the innovator drug Ritalin (methylphenidate hydrochloride). The sponsor submitted three BE studies (one pivotal in fasted condition, one in fed condition, and one comparing Methylin CT chewed versus unchewed) using highest strength tablet against reference listed drug, Ritalin tablet. The sponsor requested waiver of BE study on two lower strength tablets (2.5mg and 5mg). The sponsor has submitted sufficient information for the Office of Clinical Pharmacology and Biopharmaceutics to recommend approval. No new safety issues were revealed in these 3 studies.

### II. Chemistry

#### Drug Substance

Methylphenidate Hydrochloride USP is a white, odorless, fine crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Methylphenidate hydrochloride is methyl -phenyl-2-piperidineacetate hydrochloride, and its structural formula is



The drug substance, methylphenidate hydrochloride USP, is manufactured by Mallinckrodt Inc., at the St. Louis, Missouri facility. The address is

Mallinckrodt Inc.  
3600 North 2nd Street  
St. Louis, Missouri 63147

Drug Product  
Each Methylin® CT (methylphenidate hydrochloride chewable tablets, 2.5 mg, 5 mg and 10 mg) contains the following:

II. Quantitative Formulation

Official USP/NF  Material Name	Brand Name (Grade) and  Manufacturer's Name	%	Grams / Kg Master Blend	Strength		
				2.5 mg	5 mg	10 mg
Methylphenidate HCl USP	Code: 1571 (Mallinckrodt, Inc.)	—	—	2.5 mg	5 mg	10 mg
— Maltose						
Microcrystalline Cellulose NF *						
Guar Gum NF *						
Pregelatinized Starch NF						
Aspartame						
Grape Flavor						
Stearic Acid NF	(Mallinckrodt, Inc.)	—	—	—	—	—
TOTAL		100%	—	150 mg	300 mg	600 mg

III. Pharmacology

Methylphenidate Hydrochloride is a mild central nervous system stimulant. The mode of action in man is not completely understood, but Methylin® presumably activates the brain stem arousal system and cortex to produce its stimulant effect.

There is neither specific evidence which clearly establishes the mechanism whereby Methylin® produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

The scientific literature on the nonclinical safety of methylphenidate was examined to determine whether the findings therein meet current FDA requirements for nonclinical drug safety.

The sponsor's review of the available literature in these categories - which included the latest studies of toxicology, ADME, and pharmacology - indicates that there are no major changes in the known safety or efficacy profiles of methylphenidate.

#### **IV. Human Pharmacokinetics and Bioavailability**

The sponsor's biopharm conclusions are presented below.

##### **Study 596**

Mallinckrodt's methylphenidate chewable tablet (2 x 10 mg) test formulation is bioequivalent, when chewed or swallowed whole, in the study population of normal healthy adult male volunteers. In addition, each of these treatments is bioequivalent to a commercially available reference formulation of 20 mg methylphenidate tablet (Ritalin®, Ciba-Geigy Corporation).

##### **Study 610**

The two Mallinckrodt methylphenidate HCl formulations of chewable tablet (2 x 10 mg) and 10 mL oral solution (2 mg/mL) are well tolerated and bioequivalent to each other and to a commercially available reference formulation of 20 mg methylphenidate tablet (Ritalin®, Ciba-Geigy Corporation) in the study population of normal healthy adult male volunteers.

##### **Study 721**

The Mallinckrodt test formulation, methylphenidate HCl chewable tablet (2 x 10 mg), is bioequivalent to the reference listed drug Ritalin® tablet (Ciba-Geigy Corporation) at an equivalent dose (20 mg) when administered following a high-fat breakfast.

Please see conclusions in biopharm review of Wen-Hwei Chou, Pharm.D., Ph.D. below.

"This is a 505 (b)(2) NDA submission for Methylphenidate in a new chewable tablet (CT) formulation (2.5mg, 5.0mg, and 10mg). The sponsor submitted three BE studies (one pivotal in fasted condition, one in fed condition, and one comparing Methylin CT chewed versus unchewed) using highest strength tablet against reference listed drug, Ritalin tablet. The sponsor requested waiver of BE study on two lower strength tablets (2.5mg and 5mg). The acceptability of this NDA from the Office Clinical Pharmacology and Biopharmaceutics perspective is based on the three BE studies submitted. No clinical trials were

conducted with Methylin CT. In addition, the sponsor requests the Agency to grant a deferral of the requirement to perform pediatric studies in accordance with 21 CFR 314.55(b). The Sponsor indicated that pediatric studies (preschool age children, under age 6) are presently being conducted by the NIH which will be used to develop class labeling into the labeling proposed herein, once it is available. Overall, the sponsor has submitted sufficient information to support the approval from the Office of Clinical Pharmacology and Biopharmaceutics perspective. This is based on the bioequivalence of the 10mg tablet and granting of biowaivers for the two lower strength (2.5 and 5 mg) tablets based on the proportional similarity in composition of three tablet strengths and comparable dissolution profile. In addition, based on the submitted supportive information on the bioequivalence of chewed and unchewed Methylin CT tablet and unchewed Ritalin tablet, it is unlikely that this new chewable tablet will behave differently than reference listed product Ritalin tablet in pediatrics. Therefore, from Clinical Pharmacology perspective, granting a deferral of pediatric studies is acceptable, as is done for Methylin AQ.

The proposed label text is essentially the same as the reference listed drug product Ritalin tablet except the text that reflects change from reference listed product Ritalin to a chewable tablet dosage form. However, relevant clinical pharmacology information is lacking in current Ritalin label. In the forty-five days filing meeting, we have requested the sponsor to update label from available sources. Unfortunately, the sponsor did not propose additional labeling changes. From the Office of Clinical Pharmacology and Biopharmaceutics perspective, it is important to modify and incorporate current knowledge of methylphenidate in the Methylin CT labeling. The sponsor will be requested to update label from literature and/or other available resources. Based on available information from current submission including the three studies, literature and class labeling language from other more recent methylphenidate products (such as Concerta, methylin AQ, Metadate CD), we have suggested some relevant PK information below to be incorporated in the label.

**Recommendation:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed this NDA and finds it acceptable. Please forward "comments to the sponsor" including (1) and (2) to the sponsor. These labeling comments should be adequately addressed by the sponsor.

**Comments to the sponsor (including Phase IV commitment & detailed Label Recommendation):**

**(1) Dissolution specification:**

The selected dissolution method is acceptable. However, we recommend a change in dissolution specification for all three strengths of Methylin CT to  $Q = \sim$  in 30 minutes.

Sponsor proposed specification:  $Q = \sim$  in 45 minutes

Agency recommended specification:  $Q = \sim$  in 30 minutes

We recommend that  $Q = \sim$  in 30 minutes be accepted as interim dissolution specification for all 3 strengths of Methylin CT until additional data (described below) is submitted and reviewed.

**Phase IV commitment regarding dissolution specification:** Submit dissolution and stability data, for production batches of all three strengths (— per strength) using sponsor proposed and agency recommended dissolution specifications (i.e. 30 and 45 minutes). These batches could be next — production batches or batches currently on stability. These data should be submitted to the agency no later than 1½ years from the date of approval of this product. The sponsor should make a Phase IV commitment to submit this data for finalization of dissolution specification."

## V. Clinical Data

Clinical studies were not performed in support of this 505(b)(2) NDA. Only bioavailability / Bioequivalence studies were performed against the reference listed drug, Ritalin.

Three bioequivalence studies have been conducted 596, 610 and 721 with this dosage form. These three bioequivalence studies are:

- a) a three-way crossover bioequivalence study in the fasting state (study 596) comparing Methylin®CT chewed, Methylin®CT swallowed whole and Ritalin tablets.
- b) a three-way crossover bioequivalence study in the fasting state (Study 610), comparing Methylin®CT (Methylphenidate Hydrochloride Chewable Tablets, 10 mg), Methylin®AQ, (another new oral solution dosage form being proposed by Mallinckrodt in a separate NDA) and Ritalin® tablets, and
- c) a three-way crossover food-effect study (Study 721) of Methylin®CT (chewed, fed & fasted) vs. Ritalin® tablet (swallowed whole and fed).

There is a request for FDA deferral of the requirement to assess the safety and efficacy of methylphenidate in pediatric patients under age 6. See section VII.

The sponsor summarizes the use of methylphenidate in human patients, and gives information on its use for the treatment of ADHD and narcolepsy, based upon a review of the literature in the Medline® database. Between 1980 and 2001 there were approximately 60 review articles on the treatment of ADHD with methylphenidate and 145 articles describing clinical trials of methylphenidate for the treatment of ADHD. Over the same time period, there were approximately 65 articles that discussed the use of methylphenidate in patients diagnosed with narcolepsy. Several reports were also found that gave information on the abuse potential of methylphenidate.

The sponsor concludes that review of the current literature has confirmed that methylphenidate is safe and effective for the treatment of ADHD, in both adults and children six years of age or older, either alone or in combination with other modes of therapy, such as parental training and/or behavior modification training. They also conclude that it is also the treatment of choice for amelioration of the abnormal sleep patterns associated with narcolepsy.

Details of the three studies are provided in the appendix. I will present safety data for the three studies.

#### STUDY #721

Twenty-four (24) subjects participated in this study. One subject (721-11-008) withdrew from study participation after completion of Period 1. Twenty-three (23) subjects completed all three periods of the study. In Period 1, each subject randomly received one of three treatments:

Treatment A - Methylphenidate HCl chewable tablets (2 x 10 mg) under fasting conditions,

Treatment B - Methylphenidate HCl chewable tablets (2 x 10 mg) with food, or

Treatment C - Reference study drug Ritalin® 20 mg tablet with food.

No deaths, other serious AEs, or other significant AEs occurred during the study.

Thirteen (13) AEs were reported by 6 (25%) of the 24 subjects. Of the 13 AEs, 11 (85%) were mild in intensity and 2 (15%) were moderate in intensity. Of the 13 AEs, eight (62%) were attributed to study drug by the principal investigator.

Two events (increased hepatic enzymes, urinary tract infection), mild and moderate in intensity, respectively, were associated with Treatment A (MPH chewable tablet fasted). Of the events, one (increased hepatic enzymes) was attributed ("likely" related) to study drug and the other event (urinary tract infection) was considered "unrelated" to study drug.

Nine events [nasal congestion, nervousness, serum creatinine increased, decreased neutrophils, positive WBC in urinalysis, headache (three events), nausea], all mild or moderate in intensity, were associated with Treatment B (MPH chewable tablet with food). Of the events, five [nervousness, increased serum creatinine, headache (two events), nausea] were attributed ("likely" related) to study drug; two (positive WBC in urinalysis, headache) were "unlikely" related to study drug; one (nasal congestion) was considered "unrelated" to study drug; and one (decreased neutrophils) was considered "unassessable."

Two events (dizziness, difficulty focusing), mild in intensity, were associated with Treatment C (Ritalin® with food). Both events were attributed ("likely" related) to study drug.

Five of the individual laboratory values or changes from baseline

were considered by the principal investigator to be clinically significant.

The exit (January 22, 2001) clinical lab analysis for subject 721-11-001 indicated increased hepatic enzyme values (AST of 70, normal range 0 - 42; ALT of 63, normal range 0 - 48). At baseline, the subject's AST value was 14 and the ALT value was 17. The investigator determined that the out-of-range values were clinically significant and repeat lab samples were taken on January 26, 2001. These repeat lab values indicated that the increased values had returned to within normal limits (AST of 22, ALT of 43). The investigator considered these events "likely" related to study drug (Treatment A). The events were recorded as AEs.

The exit (January 22, 2001) clinical lab analysis for subject 721-11-003 indicated an out-of-range creatinine value of 2.0 (normal range 0.5 - 1.4). The subject's baseline value was 1.3. The investigator determined that the out-of-range value was clinically significant and a repeat lab sample was taken on January 25, 2001. The repeat lab value indicated that the out-of-range value had returned to within normal limits (1.1). The investigator considered this event "likely" related to study drug (Treatment B). The event was recorded as an AE.

The exit (January 22, 2001) clinical lab analysis for Subject 721-11-014 indicated an out-of-range value for absolute neutrophils (784, normal range 1500-7800) and a positive urinalysis WBC (10-20, normal range < 5). At baseline, the subject's absolute neutrophil count was 2856, and the urinalysis WBC was negative. The investigator determined that both out-of-range values were clinically significant and repeat lab samples were taken on January 24, 2001. These repeat lab values indicated that the absolute neutrophil count had increased to 1344 and the urinalysis WBC was negative. The investigator determined the decreased neutrophils to be of "unassessable" relationship to study drug and the positive urinalysis WBC as "unlikely" related to study drug (Treatment B). The events were recorded as AEs.

Analysis of maximum vital sign changes from baseline by treatment, category (i.e., magnitude of change), and period demonstrates no significant differences among the study drug treatments and the reference drug treatment.

#### **SAFETY SUMMARY**

Twenty-three (23) healthy adults completed all periods of the study. There were five transiently abnormal clinical laboratory values. There were no clinically significant changes from baseline in vital signs or physical examination. No serious AEs occurred during the conduct of this study.

## STUDY #610

Thirty-six (36) subjects participated in this study. Four subjects withdrew from study participation after completion of Period 1. Thirty-two (32) subjects completed both periods of the study. In Period 1, each subject randomly received one of three treatments:

Treatment A - Methylphenidate HCl chewable tablet (2 x 10 mg), chewed.

Treatment B - Methylphenidate HCl oral solution (10 mL, 2 mg/mL).

Treatment C - Reference study drug, Ritalin® (20 mg) tablet swallowed whole.

No deaths or other serious AEs occurred during the study. Three subjects dropped from the study because of adverse events.

Subject #610-11-021 dropped from the study prior to Period 2 dosing, on November 1, 2000, because of an illness that required medication. The subject took an over-the-counter medicine (Robitussion AC) and a prescription medicine (Zithromax) during the washout period following period 1 dosing for cold symptoms including cough, fever, pharyngitis, lymphadenopathy, and fatigue.

Subject #610-11-022 dropped from the study prior to Period 2 dosing, on November 4, 2000, because of an illness that required medication. The subject took over-the-counter medicines (pseudoephedrine HCl and ibuprofen) during the washout period following Period 1 dosing for cold symptoms including nasal congestion, fever, and cough.

Subject #610-11-031 withdrew from the study after he became lightheaded after the pre-dose pharmacokinetic blood sample taken for Period 2 (November 5, 2000) because he did not think he could tolerate phlebotomy for another period.

Twenty-nine (29) AEs were reported by 11 (31%) of the 36 subjects. Of the 29 AEs, 20 (69%) events were mild in intensity, 3 (10%) events were moderate, and 6 (21%) events were severe in intensity. Of the 29 events, 19 were attributed to study drug by the investigator.

Two events, (headache, constipation), both mild in severity, were temporally associated with treatment A (MPH chewable tablet). One event, headache, was attributed ("likely related") to the study drug. The other event, constipation, was considered "unlikely related."

Fourteen events [purpura, dizziness (4 events), involuntary

muscle contractions (4 events), tremor, vomiting, diaphoresis (2 events), and headache] were associated with treatment B (MPH oral solution). Of these events, 11 were attributed ("likely related") to study drug: dizziness (3 events), involuntary muscle contractions (4 events), tremor, diaphoresis (2 events), and headache. The other 3 were considered "unlikely related" to study drug. Involuntary muscle contractions (4 events), tremor, and vomiting were designated severe in intensity; the other 8 events were mild in intensity.

Thirteen events [involuntary muscle contractions, dry mouth, SGOT increased, SGPT increased, coughing (2 events), nasal congestion, pharyngitis, lymphadenopathy, fatigue, fever (2 events), headache], all mild or moderate in intensity, were associated with treatment C (Ritalin®). Of these events, 7 were attributed ("likely related") to study drug: involuntary muscle contractions, dry mouth, nasal congestion, fatigue, fever (2 events), and headache. The other 6 events were considered "unlikely related" or "unrelated."

Subject #610-11-008 experienced 4 episodes of severe involuntary muscle contractions and one episode of tremor, severe in intensity, following Period 3 dosing with treatment B (MPH oral solution). No treatment was given for these events and the subject fully recovered. The events were determined likely to be related to study drug by the principal investigator.

Subject #610-11-031 experienced 1 episode of severe vomiting following Period 1 dosing with treatment B (MPH oral solution). The subject lay down and fully recovered. The event was determined unlikely to be related to study drug by the principal investigator.

Two of the individual laboratory values were considered by the principal investigator to be clinically significant.

Subject #610-11-022 dropped from the study prior to Period 2 dosing, on November 1, 2000, because of an illness that required medication (discussed in Section 12.3 and Appendix 16.2.1). The subject returned to the clinical site for an exit physical exam and clinical labs on November 15, 2000. The exit clinical labs indicated an out-of-range AST (SGOT) value. The investigator requested that the lab be repeated; however, the subject did not comply and was lost to follow-up. The investigator determined that the laboratory value was clinically significant, mild in intensity, and unlikely related to the study drug (Treatment C, Ritalin®). The event was recorded as an AE.

The baseline clinical labs for subject #610-11-005 indicated a slightly elevated ALT (SGPT) lab value considered not clinically significant by the investigator. The exit clinical labs indicated that the ALT value had increased since baseline. The

investigator determined that the exit lab value was clinically significant and requested that the lab be repeated. The initial repeat ALT lab value was still elevated; another repeat ALT lab value, 17 days after the exit lab panel, demonstrated a return to baseline. The investigator determined that the exit ALT value was clinically significant, mild in intensity, and unlikely related to the study drug (Treatment C, Ritalin®). The event was recorded as an AE.

Analysis of maximum vital sign changes from baseline by treatment, category (i.e., magnitude of change), and period demonstrates no significant differences among the study drug treatments and the reference drug treatment.

#### **SAFETY SUMMARY**

Thirty-two (32) healthy adults completed all periods of the study. No serious AEs occurred during the conduct of this study. There were no clinically significant changes from baseline in vital signs or physical examination. There were two clinically significant out-of-range laboratory measurements.

#### **STUDY #596**

Thirty-six (36) subjects participated in this study. One subject (596-11-030) withdrew from study participation after completion of Period 1. Thirty-five (35) subjects completed both periods of the study. In Period 1, each subject randomly received one of three treatments:

Treatment A - test study drug (2 x 10 mg chewable tablets) chewed and swallowed,

Treatment B - test study drug (2 x 10 mg chewable tablets) swallowed whole, or

Treatment C - reference study drug (Ritalin® 20 mg tablet) swallowed whole.

No deaths, serious AEs, or other significant AEs occurred during this study.

One adverse event, moderate in severity, and deemed unrelated to study medication, was observed.

Subject 596-11-030 experienced an upper respiratory infection, moderate in severity, following the conclusion of Period 1. He was prescribed antibiotics and recovered. The AE was considered unlikely to be related to drug (Treatment C, reference drug) by the investigator.

None of the individual laboratory values or changes from baseline was considered by the principal investigator to be clinically significant.

Analysis of maximum vital sign changes from baseline by treatment, category (i.e., magnitude of change), and period demonstrates no significant differences among the study drug treatments and the reference drug treatment.

#### **SAFETY SUMMARY**

Thirty-five (35) healthy adults completed both periods of the study. No serious AEs occurred during the conduct of this study. There were no clinically significant changes from baseline in clinical laboratory measurements, vital signs, or physical examination.

#### **VI. Financial Disclosure**

All investigators/individuals listed on the 1572 documented that they (and their spouse or dependent children) had no financial arrangement with Mallinckrodt that could be influenced by the outcome of the study, had no proprietary interest in the study product, had no significant equity interest in Mallinckrodt exceeding \$5,000, and had not received payments from Mallinckrodt in excess of \$25,000.

#### **VII. Request for Deferral of Pediatric Study Requirement**

Mallinckrodt requests FDA to grant a deferral of the requirement to perform pediatric studies in accordance with 21 CFR 314.55(b). The grounds for this request is that pediatric studies are presently being conducted by the National Institutes of Health (NIH) which will be used to develop class labeling for pediatric use of Methylphenidate Hydrochloride. Mallinckrodt will incorporate said class labeling into the labeling proposed herein, once it is available. The labeling approved for the Reference Listed Drug, Ritalin<sup>®</sup>, and the proposed labeling herein includes the pediatric populations age 6 and above. This request, therefore, includes a request for deferral of the study of Methylphenidate Chewable Tablets in pediatric subpopulations under age 6.

#### **VIII. Labeling**

The sponsor proposed labeling for this product is essentially the same as the labeling approved for the Reference Listed Drug (RLD), Ritalin. The section ordering has been altered in accordance with 21 CFR 201.56.

No labeling changes other than the name, product description, how supplied section and company logo and information are being proposed by the sponsor in this application.

Wen-Hwei Chou, Pharm.D., Ph.D. in her review makes the following point.

**“Labeling:**

We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the pharmacokinetics of methylphenidate is lacking in the current label for the reference listed drug Ritalin as well as your proposed label for Methylin CT. We request you to update the labeling of Methylin CT to incorporate the above information from literature and/or other available resources. Based on available information from current submission including the three studies, literature and class labeling language from other more recent methylphenidate products, we suggest following relevant PK information should be added to the “Clinical Pharmacology” section of the label.”

Please see detailed labeling recommendations in biopharm review of Wen-Hwei Chou, Pharm.D., Ph.D.

**IX. Conclusions/Recommendations**

The sponsor submitted three BE studies (one pivotal in fasted condition, one in fed condition, and one comparing Methylin CT chewed versus unchewed) using highest strength tablet against reference listed drug, Ritalin tablet. The sponsor requested waiver of BE study on two lower strength tablets (2.5mg and 5mg). The sponsor has submitted sufficient information for the Office of Clinical Pharmacology and Biopharmaceutics to give approval. No new safety issues were revealed in these 3 studies.

Earl D. Hearst, M.D.

Medical Reviewer

HFD-120

cc:file\laughren\hearst\ahomonnay

**INDIVIDUAL STUDY SUMMARIES PROVIDED BY SPONSOR**

**Study 596**

**A Randomized, Two-Period Crossover, Six Sequence, Open-Label Study to Evaluate the Relative Bioavailability of a Test Tablet Formulation of Methylphenidate 10 mg Chewable (2 x 10 mg) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) Under Fasting Conditions**

<p><b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134</p> <p><b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablets</p> <p><b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl</p>	<p><b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:</p> <p>Volume:.....</p> <p>Page:.....</p> <p>Reference:.....</p>	<p><b>FOR NATIONAL AUTHORITY USE ONLY:</b></p>
<p><b>TITLE:</b> A Randomized, Two-Period Crossover, Six Sequence, Open-Label Study to Evaluate the Relative Bioavailability of a Test Tablet Formulation of Methylphenidate 10 mg Chewable (2 x 10 mg) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) Under Fasting Conditions</p>		
<p><b>PROTOCOL NO.:</b> 1137-99-596</p>		
<p><b>INVESTIGATOR/ STUDY CENTER:</b></p>		
<p><b>STUDY PERIOD:</b> Period 1 - November 19 through November 21, 1999 Period 2 - December 3 through December 5, 1999</p>		
<p><b>OBJECTIVE:</b> The objective of this study was to compare the oral bioavailability of a Mallinckrodt test formulation of methylphenidate HCl chewable tablet (either chewed or swallowed as a whole tablet) and an equivalent oral dose of the reference listed drug, Ritalin® 20 mg tablet (Ciba-Geigy Corporation), swallowed as a whole tablet, in a group of healthy subjects under fasting conditions.</p>		

<b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134  <b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablets  <b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl	<b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:  Volume:..... Page:..... Reference:.....	<b>FOR NATIONAL  AUTHORITY USE  ONLY:</b>												
<b>METHODOLOGY:</b> This was a randomized, two-period crossover, three treatment, six sequence, open-label study with an incomplete-block design in which healthy subjects randomly received two separate drug administrations separated by a washout period of at least 7 days. Drug administration consisted of two 10 mg chewable tablets of the Mallinckrodt test formulation (either chewed or swallowed as a whole tablet) or a single 20 mg tablet of Ritalin®. Blood samples (10 mL) were obtained prior to dosing and following each dose at selected time points through 24 hours. A total of 34 pharmacokinetic blood samples were collected, 17 samples in each of the two periods. Plasma was separated from the collected blood samples./ All plasma samples were analyzed for methylphenidate using a validated non-chiral LC-MS/MS analytical method, and appropriate pharmacokinetic parameters were calculated using non-compartmental methods.														
<table border="0"> <tr> <td><b>NUMBER OF SUBJECTS:</b></td> <td></td> <td><u>Age (years)</u></td> <td><u>Gender</u></td> </tr> <tr> <td>Planned (N=36)</td> <td>18-45</td> <td>Males/Females</td> <td></td> </tr> <tr> <td>Actual (N=36)</td> <td>18-41</td> <td>Males</td> <td></td> </tr> </table>			<b>NUMBER OF SUBJECTS:</b>		<u>Age (years)</u>	<u>Gender</u>	Planned (N=36)	18-45	Males/Females		Actual (N=36)	18-41	Males	
<b>NUMBER OF SUBJECTS:</b>		<u>Age (years)</u>	<u>Gender</u>											
Planned (N=36)	18-45	Males/Females												
Actual (N=36)	18-41	Males												
<b>DIAGNOSIS/INCLUSION CRITERIA:</b> Healthy, nonsmoking, male or female subjects 18 to 45 years of age, whose weight was within 15% of ideal body weight.														
<b>DOSE/ROUTE/LOT NUMBER:</b> Methylphenidate HCl 2 x 10 mg chewable tablets (Mallinckrodt Inc., Lot MHSC 9953) chewed or swallowed as a whole tablet.														
<b>REFERENCE TREATMENT:</b> Ritalin® 20 mg tablet (Ciba-Geigy Corporation, Lot 1T197606, expiration date 12/2001).														

<b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134	<b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:	<b>FOR NATIONAL  AUTHORITY USE  ONLY:</b>
<b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablets	Volume:..... Page:.....	
<b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl	Reference:.....	

**CRITERIA FOR EVALUATION:**

**Pharmacokinetics:** All pharmacokinetic plasma samples were analyzed for methylphenidate using a validated LC-MS/MS analytical method. The following pharmacokinetic parameters were calculated using standard non-compartmental analysis:

- area under the plasma concentration curve to last point (AUCt)
- area under the plasma concentration curve extrapolated to infinite time (AUCinf)
- maximum observed plasma concentration (Cmax)
- time of observed maximum plasma concentration (Tmax)
- apparent plasma terminal elimination half-life (T1/2)
- apparent first-order terminal elimination rate constant (Kel)

**Safety:** The safety of methylphenidate chewable tablet administration was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.

**STATISTICAL METHODS:**

**Pharmacokinetics:** Methylphenidate pharmacokinetic parameters were compared among the test formulation chewed, the test formulation swallowed as a whole tablet, and the reference formulation (Ritalin® 20 mg tablet) swallowed as a whole tablet. In addition, 90% confidence intervals were calculated for AUCt, AUCinf, and Cmax for each of the treatment comparisons A/B, A/C, and B/C.

**Safety:** Descriptive statistics were summarized by sequence or treatment. Number of subjects, mean, standard deviation, minimum, and maximum are presented for continuous variables; frequency distributions are presented for categorical variables. Changes from baseline values were analyzed using the one-sample Student's t-test for continuous variables and the Pearson Chi-square test for categorical variables. All statistical testing was two-sided at the 0.05 level of significance.

<b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134  <b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablets  <b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl	<b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:  Volume:..... Page:..... Reference:.....	<b>FOR NATIONAL  AUTHORITY USE  ONLY:</b>
<b>RESULTS:</b> <p><b>Pharmacokinetics:</b> Systemic exposure of methylphenidate was equivalent for the test formulation whether chewed or swallowed as a whole tablet and for the reference formulation (Ritalin® 20 mg tablet) swallowed as a whole tablet. In comparisons among all three treatments, the 90% confidence interval requirements for average bioequivalence were met for all key parameters.</p> <p><b>Safety:</b> No serious safety issues were observed. One adverse event, moderate in severity, and deemed unrelated to study medication, was observed. There were no clinically significant changes in laboratory values, vital signs, or physical examination findings.</p>		
<p><b>CONCLUSION:</b> Mallinckrodt's methylphenidate chewable tablet (2 × 10 mg) test formulation is bioequivalent, when chewed or swallowed whole, in the study population of normal healthy adult male volunteers. In addition, each of these treatments is bioequivalent to a commercially available reference formulation of 20 mg methylphenidate tablet (Ritalin®, Ciba-Geigy Corporation). Both the Mallinckrodt test formulation and the reference formulation are well tolerated.</p> <p><b>Report Date: June 12, 2001</b></p>		

III. Summary of Untransformed Pharmacokinetic Data [Mean (SD)]  
Study 596

Parameter	Treatment Groups		
	Methylin® CT Chewed (A)	Methylin® CT Unchewed (B)	Ritalin® Tablet Unchewed (C)
N	23	24	24
AUC <sub>inf</sub> (ng-hr/mL)	54.49 (29.12)	45.98 (11.36)	48.12 (25.63)
AUC <sub>t</sub> (ng-hr/mL)	53.08 (28.46)	44.51 (11.31)	46.54 (25.08)





<p><b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134</p> <p><b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablet and Methylphenidate HCl Oral Solution</p> <p><b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl</p>	<p><b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:</p> <p>Volume:.....</p> <p>Page:.....</p> <p>Reference:.....</p>	<p><b>FOR NATIONAL AUTHORITY USE ONLY:</b></p>
<p><b>TITLE:</b> An Open-Label, Randomized, Three-Way, Crossover Study to Evaluate the Relative Bioavailability of Two Test Formulations (10 mg Chewable Tablet and 2 mg/mL Liquid) of Methylphenidate Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects Under Fasting Conditions</p>		
<p><b>PROTOCOL NO.:</b> 1137-00-610</p>		
<p><b>INVESTIGATOR/ STUDY CENTER:</b></p>		
<p><b>STUDY PERIOD:</b> Period 1 – October 28 through October 30, 2000 Period 2 – November 4 through November 6, 2000 Period 3 – November 11 through November 13, 2000</p>		
<p><b>OBJECTIVE:</b> The objective of this study was to compare the oral bioavailability of two Mallinckrodt test formulations of methylphenidate HCl (chewable tablets and oral solution) to an equivalent oral dose of a commercially available methylphenidate HCl product (Ritalin® 20 mg tablet, Ciba-Geigy Corporation) in a group of healthy subjects under fasting conditions.</p>		
<p><b>METHODOLOGY:</b> This was an open-label, randomized, three-period, three-treatment, six-sequence crossover study in which healthy subjects randomly received three separate drug administrations separated by a washout period of at least 7 days. Drug administration consisted of two Mallinckrodt methylphenidate HCl chewable tablets 10 mg formulation (chewed), 10 mL (20 mg) of the Mallinckrodt 2 mg/mL methylphenidate HCl oral solution, or a single 20 mg tablet of Ritalin® swallowed whole. Blood samples (10 mL) were obtained prior to dosing and following each dose at selected time points through 24 hours. A total of 51 blood samples were collected, 17 samples in each of the three periods. Plasma was separated from the collected blood samples. All plasma samples were analyzed for methylphenidate using a validated LC-MS/MS analytical method, and appropriate pharmacokinetic parameters were calculated using non-compartmental methods.</p>		

<p><b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134</p> <p><b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablet and Methylphenidate HCl Oral Solution</p> <p><b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl</p>	<p><b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:</p> <p>Volume:.....</p> <p>Page:.....</p> <p>Reference:.....</p>	<p><b>FOR NATIONAL AUTHORITY USE ONLY:</b></p>									
<table border="1"> <thead> <tr> <th data-bbox="180 688 922 741"><b>NUMBER OF SUBJECTS:</b></th> <th data-bbox="922 688 1133 741"><u>Age (years)</u></th> <th data-bbox="1133 688 1292 741"><u>Gender</u></th> </tr> </thead> <tbody> <tr> <td data-bbox="180 741 922 783">Planned (N=36)</td> <td data-bbox="922 741 1133 783">18-48</td> <td data-bbox="1133 741 1292 783">Males/Females</td> </tr> <tr> <td data-bbox="180 783 922 831">Actual (N=36)</td> <td data-bbox="922 783 1133 831">18-46</td> <td data-bbox="1133 783 1292 831">Males</td> </tr> </tbody> </table>			<b>NUMBER OF SUBJECTS:</b>	<u>Age (years)</u>	<u>Gender</u>	Planned (N=36)	18-48	Males/Females	Actual (N=36)	18-46	Males
<b>NUMBER OF SUBJECTS:</b>	<u>Age (years)</u>	<u>Gender</u>									
Planned (N=36)	18-48	Males/Females									
Actual (N=36)	18-46	Males									
<p><b>DIAGNOSIS/INCLUSION CRITERIA:</b> Healthy, nonsmoking, male or female subjects 18 to 48 years of age, whose weight was within 15% of ideal body weight.</p>											
<p><b>DOSE/ROUTE/LOT NUMBER:</b></p> <ul style="list-style-type: none"> <li>• Methylphenidate HCl (2 × 10 mg) chewable tablets (Mallinckrodt Inc., Lot # MHSC0043).</li> <li>• Methylphenidate HCl 10 mL (2 mg/mL) oral solution (Mallinckrodt Inc., Lot # MHSC0044).</li> </ul>											
<p><b>REFERENCE TREATMENT:</b> Ritalin® 20 mg tablet, Ciba-Geigy Corporation, Lot # 1T197608, expiration date 01/02.</p>											
<p><b>CRITERIA FOR EVALUATION:</b></p> <p><b>Pharmacokinetics:</b> All pharmacokinetic plasma samples were analyzed for methylphenidate using a validated LC-MS/MS analytical method. The following pharmacokinetic parameters were calculated using standard non-compartmental analysis:</p> <ul style="list-style-type: none"> <li>• area under the plasma concentration curve to last point (AUC<sub>t</sub>)</li> <li>• area under the plasma concentration curve extrapolated to infinite time (AUC<sub>inf</sub>)</li> <li>• maximum observed plasma concentration (C<sub>max</sub>)</li> <li>• time of observed maximum plasma concentration (T<sub>max</sub>)</li> <li>• apparent plasma terminal elimination half-life (T<sub>1/2</sub>)</li> <li>• apparent first-order terminal elimination rate constant (K<sub>el</sub>)</li> </ul> <p><b>Safety:</b> The safety of methylphenidate chewable tablet and oral solution administration was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.</p>											

<p><b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134</p> <p><b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablet and Methylphenidate HCl Oral Solution</p> <p><b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl</p>	<p><b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:</p> <p>Volume:.....</p> <p>Page:.....</p> <p>Reference:.....</p>	<p><b>FOR NATIONAL AUTHORITY USE ONLY:</b></p>
<p><b>STATISTICAL METHODS:</b></p> <p><b>Pharmacokinetics:</b> Pharmacokinetic parameters were compared between the two methylphenidate HCl test formulations [<math>2 \times 10</math> mg chewable tablets (chewed) and 10 mL oral solution (2 mg/mL)] and the reference formulation - Ritalin® 20 mg tablet swallowed as a whole tablet. In addition, 90% confidence intervals were calculated for AUC<sub>t</sub>, AUC<sub>inf</sub>, and C<sub>max</sub>.</p> <p><b>Safety:</b> Descriptive statistics were summarized by sequence and/or formulation within each study period. Number of subjects, mean, standard deviation, minimum, and maximum were presented for continuous variables; frequency distributions were presented for categorical variables. Changes from baseline values were analyzed using the one-sample Student's t-test for continuous variables and the Pearson Chi-square test for categorical variables. All statistical testing was two-sided at the 0.05 level of significance.</p>		
<p><b>RESULTS:</b></p> <p><b>Pharmacokinetics:</b> Systemic exposure of methylphenidate HCl was similar for the methylphenidate HCl test formulations, <math>2 \times 10</math> mg chewable tablets (chewed) and 10 mL oral solution (2 mg/mL), as compared to the reference formulation, Ritalin® 20 mg tablet, swallowed as a whole tablet. The 90% confidence interval requirements for average bioequivalence were met for all key parameters. Bioequivalence was demonstrated among all three formulations.</p> <p><b>Safety:</b> No serious safety issues were observed. Twenty-nine (29) adverse events were reported in 11 subjects. There were no clinically significant changes in vital signs or physical examination findings. Two out-of-range laboratory values were considered clinically significant.</p>		
<p><b>CONCLUSION:</b> The two Mallinckrodt methylphenidate HCl formulations of chewable tablet (<math>2 \times 10</math> mg) and 10 mL oral solution (2 mg/mL) are well tolerated and bioequivalent to each other and to a commercially available reference formulation of 20 mg methylphenidate tablet (Ritalin®, Ciba-Geigy Corporation) in the study population of normal healthy adult male volunteers.</p> <p><b>Report Date: April 30, 2001</b></p>		

Summary of Untransformed Pharmacokinetic Data [Mean (SD)] - Study 610			
Parameter	Treatment Groups		
	Methylin <sup>®</sup> CT Tablets-Chewed (A)	Methylin <sup>®</sup> AQ Oral Solution (B)	Ritalin <sup>®</sup> Tablet Unchewed (C)
N	33	33	34
AUCinf (ng·hr/mL)	49.97 (16.28)	46.70 (15.58)	49.66 (14.80)
AUCt (ng·hr/mL)	48.32 (15.95)	45.10 (15.37)	48.01 (14.35)
Cmax (ng/mL)	9.982 (2.607)	9.075 (2.610)	9.804 (2.723)
Kel (1/hr)	0.2515 (0.0363)	0.2604 (0.0385)	0.2579 (0.0374)
T1/2 (hr)	2.826 (0.516)	2.725 (0.449)	2.756 (0.506)
Tmax (hr)	1.530 (0.413)	1.712 (0.597)	1.868 (0.432)

Reference: Tables 14.2.1-8 through 14.2.1-10 of study report for MI Protocol 1137-00- 610

Summary of 90% Confidence Intervals and CV Methylin <sup>®</sup> CT Tablets –Chewed (A) versus Methylin <sup>®</sup> AQ Oral Solution (B)						
	AUCinf	AUCt	Cmax	Kel	T1/2	Tmax
90% CI (%)	105.34-113.28	105.64-113.73	106.73-117.53	N/A*	N/A*	N/A*
LSM Ratio A/B (%)	109.24	109.61	112.00	97.01	103.44	89.91
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82

\*N/A = Not applicable  
Reference: Tables 14.2.1-11 through 14.2.1-15 of study report for MI Protocol 1137-00- 610

Summary of 90% Confidence Intervals and CV Methylin <sup>®</sup> CT Tablets –Chewed (A) versus Ritalin <sup>®</sup> Tablet (C)						
	AUCinf	AUCt	Cmax	Kel	T1/2	Tmax
90% CI (%)	99.69-107.08	99.63-107.15	100.95-111.01	N/A*	N/A*	N/A*

LSM Ratio A/C (%)	103.32	103.32	105.86	98.48	101.68	81.41
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82
*N/A = Not applicable						
Reference: Tables 14.2.1-11 through 14.2.1-15 of 15 of study report for MI Protocol 1137-00- 610						

Summary of 90% Confidence Intervals and CV Methylin <sup>®</sup> AQ Oral Solution (B) versus Ritalin <sup>®</sup> Tablet (C)						
	AUCinf	AUCt	Cmax	Kel	T1/2	Tmax
90% CI (%)	91.26-98.02	90.90-97.75	90.13-99.11	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	94.58	94.26	94.52	101.51	98.29	90.55
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82
*N/A = Not applicable						
Reference: Tables 14.2.1-11 through 14.2.1-15 of study report for MI Protocol 1137-00- 610						

V. Study 721

**An Open-Label, Randomized, Three-Way, Food Effect Study to Evaluate the Relative Bioavailability of a Test Formulation of Methylphenidate HCl 10 mg Chewable Tablet (2 x 10 mg) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin<sup>®</sup> 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects**

VI. SYNOPSIS

<b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134	<b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:	<b>FOR NATIONAL  AUTHORITY USE  ONLY:</b>
<b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablet	Volume:..... Page:.....	
<b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl	Reference:.....	

<b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134  <b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablet  <b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl	<b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:  Volume:..... Page:..... Reference:.....	<b>FOR NATIONAL  AUTHORITY USE  ONLY:</b>									
<b>TITLE:</b> An Open-Label, Randomized, Three-Way, Food Effect Study to Evaluate the Relative Bioavailability of a Test Formulation of Methylphenidate HCl 10 mg Chewable Tablet (2 x 10 mg) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects											
<b>PROTOCOL NO.:</b> 1137-00-721											
<b>INVESTIGATOR/  STUDY CENTER:</b>											
<b>STUDY PERIOD:</b> Period 1 - January 6 through January 8, 2001 Period 2 - January 13 through January 15, 2001 Period 3 - January 20 through January 22, 2001											
<b>OBJECTIVE:</b> The objective of this study was to investigate the effect of food on the oral bioavailability of a Mallinckrodt test formulation of methylphenidate HCl chewable tablet (2 x 10 mg) compared to an equivalent oral dose of Ritalin® 20 mg tablet (Ciba-Geigy Corporation) in a group of healthy subjects.											
<b>METHODOLOGY:</b> This was an open-label, randomized, three-period, three-treatment, six-sequence crossover study in which healthy subjects randomly received three separate drug administrations separated by a washout period of at least 7 days. Drug administration consisted of three treatment groups: oral administration of a 20 mg dose (2 x 10 mg) of the Mallinckrodt test formulation, methylphenidate HCl chewable tablet, in a fasted state or following a high-fat breakfast, or a single Ritalin® tablet (20 mg) swallowed whole following a high-fat breakfast. Blood samples (10 mL) were obtained prior to dosing and following each dose at selected time points through 24 hours. A total of 51 pharmacokinetic blood samples were collected, 17 samples in each of the three periods. Plasma was separated from the collected blood samples. All plasma samples were analyzed for methylphenidate using a validated non-chiral LC-MS/MS analytical method, and appropriate pharmacokinetic parameters were calculated using non-compartmental methods.											
<table border="0"> <tr> <td><b>NUMBER OF SUBJECTS:</b></td> <td><u>Age (years)</u></td> <td><u>Gender</u></td> </tr> <tr> <td>Planned (N=24)</td> <td>18 years or older</td> <td>Males/Females</td> </tr> <tr> <td>Actual (N=24)</td> <td>19-60</td> <td>18 Males/6 Females</td> </tr> </table>			<b>NUMBER OF SUBJECTS:</b>	<u>Age (years)</u>	<u>Gender</u>	Planned (N=24)	18 years or older	Males/Females	Actual (N=24)	19-60	18 Males/6 Females
<b>NUMBER OF SUBJECTS:</b>	<u>Age (years)</u>	<u>Gender</u>									
Planned (N=24)	18 years or older	Males/Females									
Actual (N=24)	19-60	18 Males/6 Females									
<b>DIAGNOSIS/INCLUSION CRITERIA:</b> Healthy, nonsmoking, male or female subjects 18 years of age or older, whose weight was within 15% of ideal body weight.											

<p><b>NAME OF COMPANY</b> Mallinckrodt Inc. 675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134</p> <p><b>NAME OF FINISHED PRODUCT</b> Methylphenidate HCl Chewable Tablet</p> <p><b>NAME OF ACTIVE INGREDIENT</b> Methylphenidate HCl</p>	<p><b>SUMMARY TABLE</b> Referring to Part ..... of the Dossier:</p> <p>Volume:.....</p> <p>Page:.....</p> <p>Reference:.....</p>	<p><b>FOR NATIONAL AUTHORITY USE ONLY:</b></p>
<p><b>DOSE/ROUTE/LOT NUMBER:</b> Methylphenidate HCl (2 × 10 mg) chewable tablet (Mallinckrodt Inc., Lot MHSC0043).</p>		
<p><b>REFERENCE TREATMENT:</b> Ritalin® 20 mg tablet (Ciba-Geigy Corporation, Lot 1T197608, expiration date 01/2002).</p>		
<p><b>CRITERIA FOR EVALUATION:</b></p> <p><b>Pharmacokinetics:</b> All pharmacokinetic plasma samples were analyzed for methylphenidate using a validated LC-MS/MS analytical method. The following pharmacokinetic parameters were calculated using standard non-compartmental analysis:</p> <ul style="list-style-type: none"> <li>• area under the plasma concentration curve to last point (AUC<sub>t</sub>)</li> <li>• area under the plasma concentration curve extrapolated to infinite time (AUC<sub>inf</sub>)</li> <li>• area under the plasma concentration curve to median T<sub>max</sub> value of reference treatment (AUC<sub>tmx</sub>)</li> <li>• maximum observed plasma concentration (C<sub>max</sub>)</li> <li>• time of observed maximum plasma concentration (T<sub>max</sub>)</li> <li>• apparent plasma terminal elimination half-life (T<sub>1/2</sub>)</li> <li>• apparent first-order terminal elimination rate constant (K<sub>el</sub>)</li> </ul> <p><b>Safety:</b> The safety of methylphenidate chewable tablet was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.</p>		

<p><b>NAME OF COMPANY</b>  Mallinckrodt Inc.  675 McDonnell Blvd.  P.O. Box 5840  St. Louis, MO 63134</p> <p><b>NAME OF FINISHED PRODUCT</b>  Methylphenidate HCl Chewable  Tablet</p> <p><b>NAME OF ACTIVE INGREDIENT</b>  Methylphenidate HCl</p>	<p><b>SUMMARY TABLE</b>  Referring to Part  .....  of the Dossier:</p> <p>Volume:.....</p> <p>Page:.....</p> <p>Reference:.....</p>	<p><b>FOR NATIONAL  AUTHORITY USE  ONLY:</b></p>
<p><b>STATISTICAL METHODS:</b></p> <p><b>Pharmacokinetics:</b> Methylphenidate pharmacokinetic parameters were computed for the test product methylphenidate HCl chewable tablet (2 × 10 mg) when administered under fasting conditions (Treatment A) or administered following a high-fat breakfast (Treatment B), and for the reference formulation, Ritalin® 20 mg tablet, orally administered following a high-fat breakfast (Treatment C). The bioequivalence of the test and reference formulations in the fed state and the effect of food on methylphenidate pharmacokinetics was examined. In addition, 90% confidence intervals were calculated for AUCt, AUCinf, AUCtmx, and Cmax between the comparative treatments B/A, B/C and C/A.</p> <p><b>Safety:</b> Descriptive statistics were summarized within each study period by sequence and/or formulation. Number of subjects, mean, standard deviation, minimum, and maximum are presented for continuous variables; frequency distributions are presented for categorical variables. Changes from baseline values were analyzed using the one-sample Student's t-test for continuous variables and the Pearson Chi-square test for categorical variables. All statistical testing was two-sided at the 0.05 level of significance.</p>		
<p><b>RESULTS:</b></p> <p><b>Pharmacokinetics:</b> Systemic exposure to methylphenidate HCl was equal for the Mallinckrodt Inc. test formulation methylphenidate HCl chewable tablet (2 × 10 mg) as compared to the reference listed drug, Ritalin® (20 mg tablet), when administered following a high-fat breakfast (fed condition). The 90% confidence interval requirements for average bioequivalence were met for all key parameters for the test/reference formulation comparison under the fed condition. When given with food, a statistically significant increase in AUCinf, AUCt, and Tmax was observed. The effect of food appears equivalent for both formulations.</p> <p><b>Safety:</b> Thirteen (13) adverse events were reported by six subjects. There were five transiently abnormal clinical laboratory values. There were no clinically significant changes in vital signs or physical examination findings. No serious safety issues were observed.</p>		

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<b>CONCLUSION:</b> The Mallinckrodt test formulation, methylphenidate HCl chewable tablet (2 × 10 mg), is bioequivalent to the reference listed drug Ritalin® tablet (Ciba-Geigy Corporation) at an equivalent dose (20 mg) when administered following a high-fat breakfast. Administration of the chewable tablet with food appeared to result in increased and prolonged absorption relative to the fasted state. All treatments were well tolerated.  <b>Report Date: June 6, 2001</b>		

Summary of Untransformed Pharmacokinetic Data [Mean (SD)] - Study 721			
Parameter	Treatment Groups		
	Methylin® CT Tablets Fasting (A)	Methylin® CT Tablets With Food (B)	Ritalin® Tablet With Food (C)
N	23	23	24
AUC <sub>inf</sub> (ng-hr/mL)	56.37 (25.64)	66.96 (29.65)	66.75 (27.66)
AUC <sub>t</sub> (ng-hr/mL)	54.23 (24.49)	65.01 (29.13)	65.00 (27.16)
AUC <sub>tmx</sub> (ng-hr/mL)	14.05 (4.93)	12.21 (3.87)	13.43 (6.81)
C <sub>max</sub> (ng/mL)	11.041 (3.970)	11.055 (3.308)	12.979 (4.429)
K <sub>el</sub> (1/hr)	0.2438 (0.0540)	0.2520 (0.0394)	0.2510 (0.0388)
T <sub>1/2</sub> (hr)	3.047 (1.032)	2.824 (0.500)	2.828 (0.456)
T <sub>max</sub> (hr)	1.489 (0.443)	2.413 (0.718)	2.167 (0.940)
Reference: Tables 14.2.1-8 through 14.2.1-10 of study report for MI Protocol 1137-00- 721 AUC <sub>tmx</sub> = AUC <sub>0-2</sub>			

**Summary of 90% Confidence Intervals and CV Methylin® CT Tablets with Food (B) versus Methylin® CT Tablets Fasting (A)**



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/s/  
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Earl Hearst  
9/19/02 02:12:35 PM  
MEDICAL OFFICER

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Laughren  
9/19/02 10:53:19 AM  
MEDICAL OFFICER

I agree that, from a clinical standpoint, this NDA  
is approvable; see memo to file for more  
detailed comments.--TPL