CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-419

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

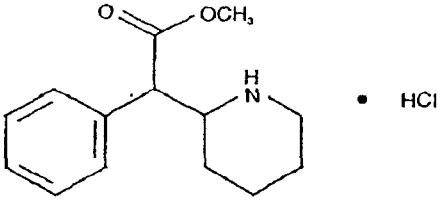
NDA 21-419
Sponsor: Mallinckrodt Inc.
Drug: Methylin® [redacted] Methylphenidate Hydrochloride Oral Solution)
Material Submitted: NDA submission for 505(b)(2) application
Related NDAs: Ritalin® (NDA 10-187 Novartis)
Ritalin® SR (NDA 18-029 Novartis)
Ritalin® LA (NDA 21-284 Novartis)

I. Summary

Methylin® [redacted](methylphenidate hydrochloride oral solution) 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). This submission includes only two single dose pharmacokinetic and bioequivalence studies in adults. Therefore, the clinical safety data for this NDA is very limited, and no unexpected findings were observed. The sponsor has requested a waiver to defer testing in the pediatric subpopulation under age 6 years old. The sponsor's proposed labeling is based on an outdated version of the Ritalin® labeling, and requires much revision to reflect more recent modifications.

II. Chemistry

The chemical structure for methylphenidate is:



The chemical name is methyl ∝-phenyl-2-peperidineacetate hydrochloride. The proposed drug substance is a colorless, grape flavored liquid with proposed concentrations of 5 mg/5mL and 10 mg/5 mL.

Inactive ingredients include: citric acid, annhydrous USP, Glycerin USP, N&A Grape Flavor, PEG 1450 NF, and Purified Water USP.

The chemistry review identified impurities which the sponsor had not characterize in the original submission. Please refer to the chemistry review for further details.

The sponsor has proposed the trade name of Methylin® [redacted]

III. Pharmacology

References to previously conducted studies were cited in this submission. The sponsor has not yet conducted any new pre-clinical studies to support this application. It is unclear at this point in the review if the sponsor will be required to perform toxicology studies to qualify the identified impurities.

IV. Human Pharmacokinetics and Bioavailability

There were two studies conducted to assess the human pharmacokinetics and bioavailability; both studies were conducted in adults and were single dose only. Study 610 was a three way crossover bioequivalence study in the fasting state comparing Methylin®, [redacted] Methylin®CT 10 mg and Ritalin® 20 mg tablet. Study 722 was a three way crossover food-effect study of Methylin®, [redacted] (in fasting and fed states) with Ritalin® 20 mg tablet (fed).

Below is the sponsor's summary table of pharmacokinetic findings in the current submission.

Table 4.2.1: Summary of Methylphenidate Pharmacokinetics in the Mallinckrodt Dosage Forms and Comparison Reported Values

Study	Treatment	AUCinf (ng·hr/mL)	AUCt (ng·hr/mL)	AUCtmx (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	Kel (1/hr)	$T_{1/2}$ (hr)	Comments
610	MPH CT (2x10 mg) Chewed, Fasting	49.97 (16.28)	48.32 (15.95)	Not Determined	9.982 (2.607)	1.530 (0.413)	0.2515 (0.0363)	2.826 (0.516)	Under fasting conditions Methylin® CT, Methylin® [redacted] and Ritalin® Tablets were bioequivalent to each other. Pharmacokinetic parameters were very similar between all three treatments with very slight differences that do not warrant any adjustments in dosing.
	MPH [redacted] (10 mL, 2 mg/mL) Fasting	46.70 (15.58)	45.10 (15.37)	Not Determined	9.075 (2.610)	1.712 (0.597)	0.2604 (0.0385)	2.725 (0.449)	
	Ritalin® tablet (20 mg) Swallowed, Fasting	49.66 (14.80)	48.01 (14.35)	Not Determined	9.804 (2.723)	1.868 (0.432)	0.2579 (0.0374)	2.756 (0.506)	
722	MPH [redacted] (10 mL, 2 mg/mL) Fasting	51.91 (24.73)	50.27 (23.73)	15.65 (5.21)	9.391 (3.626)	1.707 (0.444)	0.2411 (0.0346)	2.537 (0.614)	Statistically significant food effect was observed. In the Fed State the Methylin® [redacted] was bioequivalent to the reference listed drug product. The observed food effect was concluded to be indeterminate according to draft FDA guidance.[4]
	MPH [redacted] (10 mL, 2 mg/mL) with Food	64.95 (25.21)	62.65 (23.54)	14.79 (4.83)	10.693 (2.639)	2.667 (0.747)	0.2477 (0.0408)	2.563 (0.310)	
	Ritalin® tablet (20 mg) Swallowed with Food	68.71 (26.52)	66.24 (25.33)	15.71 (6.42)	12.079 (3.477)	2.438 (0.812)	0.2401 (0.0483)	2.673 (0.505)	
Reported	(+)-threo-MPH after 20 mg oral dosing of racemic MPH[12]	5.9-47.2	N/A	N/A	1.7-12.5	1-3		2.6-3.3	Significant correlation (r=0.850) observed between plasma concentrations vs sleep latency test. No correlation observed plasma concentrations vs subjective sleepiness

Please refer to the biopharmaceutics review by Wen-Hwei Chou, Pharm,D., Ph.D. for a detailed review of the submitted data. Briefly, Methylin [redacted] was found to be easily absorbed with a tmax of 1-2 hours and a mean half life of 2.7 hours compared to Ritalin's half life of 2.8 hrs. There was a food effect observed for Methylin® [redacted] which resulted in delayed absorption of methylphenidate by approximately 1 hour. Dr. Chou's preliminary review concluded that the sponsor was able to demonstrate bioequivalence to the reference table of Ritalin®.

V. Clinical Data

The only studies submitted to support this application are the two pharmacokinetic studies 610 and 722 described in more detail below in this section. To date, there have been no studies conducted in the pediatric population for pharmacokinetics. No efficacy or multiple dose safety studies have been conducted for this aqueous methylphenidate.

Study 610

Study 610 was a open label, three way crossover bioequivalence study in the fasting state comparing a single dose of Methylin®, 20 mg (in 10 ml liquid), Methylin®CT 20 mg (2 chewable 10 mg tablets) and Ritalin® (20 mg tablet). There was a wash out period of at least 7 days between dose administrations. Included in the study were healthy adults aged 18-48 y.o. Screening included a history and physical, ECG, routine labs, HIV testing, hepatitis screen, and urine drug screen. Vitals and blood levels for pharmacokinetics (at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24 hours post dosing) were collected during the study. Labs were repeated at the conclusion of the study after the entire sequence of dosing.

Demographics showed that 36 males with a mean age of 26 years old (age range 18-46) participated in the study. The majority were Caucasian with the following racial breakdown:

Asian: n=1 (3%)
Afro-American: n=5 (14%)
White: n=30 (83%)

Of the 36 patients who began the study, 32 patients completed. The four withdrawals included the following:

1) One subject (#610-11-031) withdrew because of the adverse event of becoming lightheaded after the pre-dose blood samples and decided to not continue into the second period.
2) One subject (#610-11-013) withdrew for personal reasons (mother was in a car accident), and
3) Two subjects (#610-11-021 & #610-11-022) withdrew because they required medication and pseudoephedrine) for illnesses during the washout period.

Adverse events associated with the use of MPH oral solution (Methylin®) included the following: 1) severe in intensity: involuntary muscle contractions (4 events in 1 subject), tremor, vomiting, and headache, 2) mild in intensity: purpura, diaphoresis (2 events in 1 subject), and dizziness (3 events occurring in 2 subjects). The following table summarizes all adverse events reported in Study 610after administration of each drug.

Adverse events observed in Study 610 after single doses.

SEVERITY	METHYLIN CHEWABLE N=33	METHYLIN LIQUID N=33	RITALIN N=34
Severe			
Muscle contractions, Involuntary		1 (3%)	
Tremor		1 (3%)	
Vomiting		1 (3%)	
Moderate			
Coughing			2 (6%)
Nasal congestion			1(3%)
Mild			
Constipation	1 (3%)		
Headache	1 (3%)	1 (3%)	1 (3%)
Muscle contractions, Involuntary			1 (3%)

Purpura		1 (3%)	
Diaphoresis		1 (3%)	
Dizziness		2 (6%)	
Dry mouth			1 (3%)
Fever			2 (6%)
Increased SGOT			1 (3%)
Increased SGPT			1 (3%)
Pharyngitis			1 (3%)
Lymphadenopathy			1 (3%)
Fatigue			1 (3%)

Laboratory values were obtained at the beginning and at the end of the study, and were not recorded after each individual treatment. There were only two laboratory incidences of note. One subject (#610-11-022) had an elevated SGOT (AST) from 25 U/L to 96 U/L (normal:0-42 U/L) after one dose of Ritalin; this was complicated by the fact that the subject had taken concomitant medications for an illness prior to the blood draw and subsequently withdrew from the study. Another subject (#610-11-005), whose last sequential dose was Ritalin, had an elevated SGPT (ALT) from 57 U/L to 73 U/L (NL:0-48 U/L), and then a return to his baseline after 17 days. It is noted that interpretations of results based on a series of single doses are difficult to interpret and difficult to attribute to any one of the study drugs administered.

A review of the vital signs showed an increase in mean heart rate and blood pressure (systolic and diastolic) after dosing of Methylin® ━ These are results that are not unexpected after dosing with methylphenidate. Below is a summary table of findings after the dosing of Methylin® ━

Study 610: Summary of statistically significant vitals immediately after Methylin® ━ dosing (based on sponsor's table 12.5.1-1)

Dosing sequence of Methylin® ━	Parameter	Time Post dose (hrs)	N	Mean change from baseline (SD)
Period One	Systolic BP	2 hr	6	8.8 (7.5)
	" "	6	6	13.3 (11.6)
	Pulse	6	6	9.7 (5.1)
	Systolic BP	2	5	6.0 (3.2)
	" "	4	5	6.6 (4.5)
Period Two	Pulse	2	5	8.0 (6.1)
	" "	4	5	13.8 (3.8)
	Diastolic BP	6	5	-7.4 (4.5)
	Pulse	6	5	7.4 (3.7)
Period Three	Diastolic BP	Exit	6	5.7 (3.9)
	Systolic BP	6	6	8.7 (2.1)
	Pulse	6	6	12.8 (9.7)
	Pulse	6	5	17.4 (13)

Study 722

This was an open label, three way crossover, food-effect study of Methylin® 20 mg (10 mg of 2 mg/ml) in fasting and fed states compared with Ritalin® 20 mg tablet (fed). Each drug administration was separated by a washout period of at least 7 days.

Included in the study were healthy adults aged 18-48 y.o. Screening included a history and physical, ECG, routine labs, HIV testing, hepatitis screen, and urine drug screen. Vitals and blood levels for pharmacokinetics (at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 24 hours post dosing) were collected during the study. Labs were repeated at the conclusion of the study after the entire sequence of dosing.

There was one withdrawal: subject #722-11-041 withdrew because of adverse event of myalgia; he wasn't administered the 3rd period mediation (was exposed to Methylin® and then Ritalin).

Demographics showed that 24 subjects (19 males and 5 females) with a mean age of 28.5 years old (age range 19-65) participated in the study. All patients were Caucasian.

There were no unexpected adverse events occurring in this data base. Below is a summary table of all adverse events observed after administration of each drug.

Adverse events observed in Study 722.

	METHYLIN LIQUID (FASTING) N=23	METHYLIN LIQUID (FED) N=24	RITALIN N=24
Headache	1	2	1
Nausea		1	
Myalgia			1
Rash			1

Laboratory values were obtained at the beginning and at the end of the study, and were not recorded after each individual treatment; therefore, the results are difficult to interpret and difficult to attribute to any one of the study drugs administered. However, it is noted that there were no clinically significant changes in laboratory results reported.

A review of the vital signs showed an increase in mean heart rate and blood pressure (systolic and diastolic) after dosing of Methylin® These are results that are not unexpected after dosing with methylphenidate. Below is a summary table of findings after the dosing of Methylin®

Study 722: Summary of statistically significant vital signs immediately after Methylin® dosing (based on sponsor's table 12.5.1-1)

Dosing sequence of Methylin®	Parameter	Time Post dose (hrs)	N	Mean change from baseline (SD)
Period One	Systolic BP	4 hr	4	3.5 (1.0) mmHg
	" "	6	3	13.0 (3.6)
	Pulse	2	4	14.5 (5.2) bpm
	" "	6	4	12.0 (6.6)

	" "	2	3	24.7 (3.2)
	" "	6	3	20.3 (1.5)
Period Two	Systolic BP	4	4	7.3 (3.9) mmHg
	Pulse	6	4	17.5 (10) bpm
Period Three	Systolic BP	6	4	11.0 (5.9) mmHg
	" "	6	4	11.3 (5.7)
	Diastolic BP	6	4	5.5 (3.0)
	Pulse	2	4	19.5 (9.8) bpm
	" "	2	4	19.0 (11.2)
	" "	6	4	13.3 (7.6)

VI. Financial Disclosure

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Vice President of Regulatory & Clinical Affairs at Malinkrodt signed the Form 3454 testifying that, to his knowledge, there was no financial arrangement made with investigators that could affect the outcome of the studies as defined in 21 CFR 54.2 (a), and that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). One individual investigator did not properly fill out the form regarding financial arrangement; however, the sponsor has included this investigator in the list of investigators which the sponsor has not entered into any financial arrangement as described in 21 CFR 54.2.

VII. Request for Deferral of Pediatric Study Requirement

The sponsor has requested to defer studies in the pediatric population younger than 6 years of age.

VIII. Labeling

The proposed labeling is modeled after an outdated version of the innovator drug, Ritalin®. It is recommended that the labeling be revised to incorporate an updated labeling format utilized in recently marketed methylphenidate-related products; significant revisions were made to the following sections: Clinical Pharmacology, Indications and Usage, Contraindications, Warnings, Precautions, Carcinogenesis, Usage in Pregnancy, Nursing Mothers, Pediatric Use, and Overdosage. It is also recommended that the sponsor's labeling include pharmacokinetic data submitted in this recent submission (please refer to the FDA biopharmaceutics review by Wen-Hwei Chou, Pharm.D., Ph.D.).

IX. Conclusions/Recommendations

There were no unexpected adverse events observed in the data base submitted for this NDA. However, the data submitted was limited to single doses only in the adult population, and does not necessarily generalize to effects observed with multiple doses. Ideally, the sponsor would have collected data also in the pediatric population 6 years old and above, which is the presumed target population; however, from a regulatory stand point, it is not required, because the sponsor may rely on the safety data and history of the reference drug Ritalin®. At this time, it would be appropriate for FDA to defer the clinical studies for the population less than 6 years old until the methodology for conducting studies and appropriate end points in the preschool age group is better established.

From a clinical regulatory perspective, there are no objections for the approval of Methlyn®/— It is recommended that the sponsor consider conducting studies in the pediatric population, which is the intended target population, for more specific information regarding safety and pharmacokinetics. It is also recommended that the sponsor perform any toxicology studies recommended for the identified impurities.

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NDA 20-825
Div File
HFD-120: Katz/Laughren/Homonnay/Glass

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APPEARS THIS WAY
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