CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-419

CHEMISTRY REVIEW(S)

NDA 21-419

METHYLIN — (Methylphenidate HCl Oral solution)

Mallinckrodt Inc.

Christy S. John, Ph.D.
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-419

2. Review # 1

3. REVIEW DATE: May 28, 2002

4. Reviewer: Christy S. John

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	08/03/2001
Telecon	04/15/2002
IR Letter	04/23/2002
Additional Data	05/17/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt Inc
Address:	675 McDonnell Boulevard, P.O. Box 5840, St. Louis MO 63134
Representative:	Ronald T. Groman, Manager, Regulatory Affairs
Telephone:	(314)-654-6060

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Methylin®
b) Established Name, USP/USAN name: Methylphenidate Hydrochloride Oral Solution
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Attention Deficit Disorder, Narcolepsy

11. DOSAGE FORM: Liquid

12. STRENGTH/POTENCY: 5 mg/5 mL and 10 mg/5 mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

_____SPOTS product – Form Completed

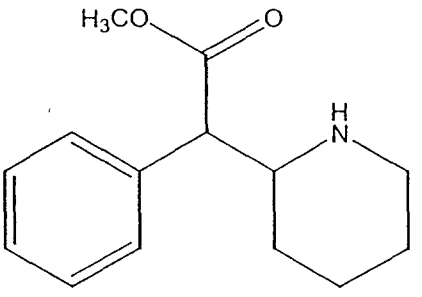
___X___Not a SPOTS product

16. CHEMICAL NAME: Methyl α–phenyl-2-piperidineacetate hydrochloride

MOLECULAR FORMULA: $C_{14}H_{19}NO_2.HCl$

MOLECULAR WEIGHT: 269.77

STRUCTURAL FORMULA:



.HCL

17. RELATED/SUPPORTING DOCUMENT:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	[3]DATE REVIEW COMPLETED	COMMENTS
12769		Mallinckrodt Inc.	Methylphenidate.HCl			04/21/00	Adequate
[redacted]						08/15/98	Adequate
[redacted]						12/13/99	Adequate
[redacted]						11/23/94	Adequate
[redacted]						05/11/00	Adequate
[redacted]						05/18/99	Adequate
[redacted]						12/13/99	Adequate

		03/22/01	Adequate
		02/16/2000	Adequate

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

APPEARS THIS WAY
ON ORIGINAL

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	September 14, 2001	Office of Compliance
Pharm/Tox	Pending		Ed Fisher, Ph.D.
Biopharm	Acceptable	04/24/02	
LNC			
Methods Validation	To be submitted		
OPDRA	[redacted]		
EA	Categorical exclusion	03/08/01	Christy John, Ph.D.
Microbiology	N/A		

OGD: N/A

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

Executive Summary Section

The Chemistry Review for NDA 21-419

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate information on chemistry, manufacture and controls of the drug product to assure its identity, strength, quality and purity. The facilities involved in the manufacturing and controls of drug substance and drug product were found to be acceptable by the Office of Compliance. This application may be approved from the CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Methylin [redacted] (Methylphenidate Hydrochloride Oral Solution) 5 mg/5 mL and 10 mg/5 mL CII is a clear, colorless to [redacted] solution with a grape odor formulated for attention deficit disorder. Both strengths are available in 250 mL and 500 mL [redacted] bottles with white [redacted] caps and a [redacted] foil seal.

Methylphenidate Hydrochloride,USP (drug substance) is a white, odorless, fine crystalline powder. Its aqueous solutions are acidic to litmus. It is freely soluble in water and methanol, soluble in alcohol, and slightly soluble in chloroform and acetone. Methylphenidate hydrochloride is methyl-phenyl-2-piperidineacetate hydrochloride. The drug substance, methylphenidate hydrochloride USP, is manufactured by Mallinckrodt Inc. in St. Louis, Missouri. The full details of the chemistry, manufacturing, characterization, stability, and controls used in the production of Methylphenidate Hydrochloride USP, are referred to Mallinckrodt's Drug Master File (DMF) #12769.

The manufacturing process of the drug product is simple and is based upon the solubility of the different components in water. The chemical components of both strengths includes the following: citric acid anhydrous, USP; glycerin, USP; grape flavor [redacted] ; methylphenidate hydrochloride, USP; polyethylene glycol 1450, NF; and purified water, USP.

The proposed product will be packaged in 8 ounce (250 mL) and 16 ounce (500 mL) [redacted] bottles with [redacted] caps. The cap liner for the 8 ounce bottle is a [redacted]

The stability data for both strengths and bottle sizes shows that the product is quite stable under room temperature (25 °C/60%RH) conditions, but undergoes considerable degradation under accelerated (40 °C/75%RH) conditions.

Two new impurities Related Substance A and Related Substance B are formed in the product as a result of reaction between methylphenidate and [redacted] The degradation product Related Substance A increased from less than [redacted] to as much as [redacted] to methylphenidate, exceeding [redacted] upper limit in both strengths. The Total Related Substances levels exceeded the [redacted] specification after six months at 40 °C/75%RH in the 5 mg/5 mL strength and in one of the 10 mg/5 mL strengths.

Other trends observed over the six month 40 °C/75%RH test period included about [redacted] decrease in methylphenidate HCl concentration. A corresponding increase in the primary degradation product, [redacted] also occurred at 40 °C/75% RH, increasing from [redacted] with respect to methylphenidate HCl in both strengths.

The stability protocol under which the tests were conducted calls for samples to be taken from an intermediate condition, 30 °C/60%RH, if the 40 °C/75%RH samples fail to meet specification. Accordingly, samples from the two lots that had stability failures at the six month 40 °C/75%RH intervals were tested at twelve months 30 °C/60%RH condition. All stability parameters were well within specification although similar trends were observed with methylphenidate HCl, [redacted] and Related Substances A and B. These results indicate that Methylin [redacted] is a labile product and prone to decomposition with time in the presence of heat and humidity. It is therefore, recommended that an expiration dating of 18 month is more appropriate at this point than the [redacted] as requested by the applicant.

In conclusion, the new impurities of Related Substance A and B are of concern to this reviewer. These impurities have now been completely characterized at the request of this reviewer. However, no experimental data is available on these impurities regarding the toxicological profiles in animals.

APPEARS THIS WAY
ON ORIGINAL

B. Description of How the Drug Product is Intended to be Used

The Methylin product is to be marketed in two concentrations (5 mg/5 mL and 10 mg/5 mL) and each concentration is packaged in two containers; 250 mL and 500 mL. The two strengths are identical except for the concentration of methylphenidate HCl.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate information on chemistry, manufacture and controls of the drug product to assure its identity, strength, quality and purity. The facilities involved in the manufacturing and controls of drug substance and drug product were found to be acceptable by the Office of Compliance. This application may be approved from the CMC standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

JOHNCS/05/23/02
PATELH/05/23/02
HOMONNAYAM

APPEARS THIS WAY
ON ORIGINAL

(F)

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

20 pages

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

/s/

Christy John
5/29/02 01:40:53 PM
CHEMIST

Hasmukh Patel
5/29/02 01:50:44 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

NDA 21-419

Methylin Oral Solution
(Methylphenidate Hydrochloride Oral Solution)

Mallinckrodt Incorporated

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-419 Methylin Oral Solution (Methylphenidate Hydrochloride Oral Solution)**

2. **CMC REVIEW: #2**

3. **REVIEW DATE:** December 16, 2002

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** CMC Review # 1 dated 29-MAY-02

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
Amendment-(AZ)	31-OCT-02

7. **NAME AND ADDRESS OF APPLICANT:**
   Mallinckrodt Inc.
   675 McDonnell Blvd
   P.O. Box 5840
   St. Louis, MO 63134-0840

8. **DRUG PRODUCT NAME:**
   Proprietary: Methylin Oral Solution (Methylphenidate Hydrochloride Oral Solution)
   Nonproprietary/USAN: methylphenidate hydrochloride
   Code Name/Number: none
   Chem. Type/Ther. Class: 3S

9. **LEGAL BASIS FOR SUBMISSION:** 505(b)(2)

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** ADHD, Narcolepsy

11. **DOSAGE FORM:** Solution

12 **STRENGTHS:** 5 mg per 5 mL; and 10 mg per 5 mL

13. **ROUTE OF ADMINISTRATION:** Oral

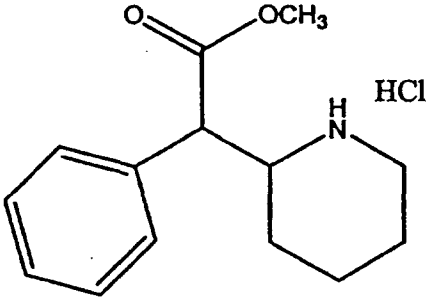
14. **DISPENSED:** XX RX ___OTC

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___ Yes XX NO

APPEARS THIS WAY
ON ORIGINAL

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
methyl α-phenyl-2-piperidineacetate hydrochloride

Molecular formula: $C_{14}H_{19}NO_2$. HCl
Mol. Wt. 269.77
CAS Registry # 298-59-9



17. **RELATED/ SUPPORTING DOCUMENTS:**
A. **DMF's:**

12769	II	Mallinckrodt	Methylphenidate HCl	1	Adequate	21-APR-2000	Drug substance
	III			1	Adequate	15-AUG-1998	
	III			1	Adequate	28-SEP-2000	
	III			1	Adequate	23-NOV-1994	
	III			1	Adequate	11-MAY-2000	
	III			1	Adequate	18-MAY-1999	
	III			1	Adequate	22-MAR-2001	
	III			1	Adequate	16-FEB-2000	

[1]Action codes for DMF Table:
1--DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2--Type 1 DMF
3--Reviewed previously and no revision since last review
4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7--Other (explain under "Comments")

[2]Adequate, Inadequate

B. Other Documents:

NDA 10-187	Novartis	5-DEC-1955

18. **STATUS:**

EES	Acceptable	12-NOV-02	Office of Compliance
Methods Validation	To be submitted		Donald N. Klein, Ph.D.
Clinical	Approval	16-MAY-02	Roberta Glass, M.D.
Microbiology	N/A	29-MAY-02	Christy John, Ph.D.
OCPB/Bioequivalence	Approval	24-APR-02	Wen-Hwei Chou, Pharm.D.,Ph.D.
EA	Approval	29-MAY-02	Christy John, Ph.D.
OPDRA	Proposed [redacted]	19-DEC-01	Hye-Joo Kim, Pharm.D.
CSS	Revisions of the proposed labeling	24-APR-02	Ann-Kathryn Maust, M.D.
Pharm/Tox	pending		Edward Fisher, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-419 for Methylin Oral Solution (Methylphenidate Hydrochloride Oral Solution) is recommended for Approval from the CMC standpoint.

B. Recommendations on Phase 4(Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

The following analytical methods were revised and submitted in this response because the applicant had previously reported (refer to CMC Review #1 dated 5/29/02) the incorrect data of both the Related Substance A and B. The response factor error is reported in this response (page 7, 10/31/02). The correct analytical data are reported in this response (10/31/02).

1. **Method M-43-C**: For Finished Product Release only, 10 mg/5 mL
2. **Method S-M-29C**: For Stability Testing Only, 10 mg/5 mL
3. **Method S-M-28D**: For Stability Testing Only, 5 mg/5 mL
4. **Method M-41-C**: For Finished Product Release only, 5 mg/5 mL

These analytical methods were revised to reflect the response factor of Related Substance A and B. The revised methods will be submitted to the FDA lab for validation.

The drug product stability data (outlined in Table 5 in this review) meets the proposed specifications through 18 months at 25°C/60%RH.

The drug product (5mg/5mL and 10mg/5mL) expiration date is 18 months at 25°C/60%RH.

The drug product sites were found Acceptable by Compliance.

Drug Substance

Methylphenidate Hydrochloride, USP is referenced in DMF 12769, Type II, which was found Adequate by Donald N. Klein, Ph.D. (HFD-120) on April 29, 2000. The Holder of

DMF 12769 is Mallinckrodt Inc.

The drug substance site was found Acceptable by Compliance.

B. Description of How the Drug Product is Intended to be Used

The Methylin Oral Solution will be marketed as follows:

1. 5mg/5mL concentration in 250 mL natural colored, — oblong bottle with a Child-Resistant Closure.
2. 10mg/5mL concentration in 250 mL natural colored, — oblong bottle with a Child-Resistant Closure.
3. 5mg/5mL concentration in 500 mL white oblong, — bottle with a Child-Resistant Closure.
4. 10mg/5mL concentration in 500 mL white oblong, — bottle with a Child-Resistant Closure.

The drug product (5mg/5mL and 10mg/5mL) expiration date is 18 months at 25°C/60%RH.

C. Basis for Approvable or Not-Approval Recommendation: N/A

D. Administrative:
Reviewer: Donald N. Klein, Ph.D.
Team Leader: Thomas F. Oliver, Ph.D.
Project Manager: Anna Marie Hommonay-Weikel, R.Ph.

APPEARS THIS WAY
ON ORIGINAL

E

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

11

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21419/000
Org Code : 120
Priority : 3S

Sponsor: MALLINCKRODT BAKER
675 MCDONNELL BLVD
ST LOUIS, MO 63134

Stamp Date : 02-AUG-2001
PDUFA Date : 31-DEC-2002
Action Goal :
District Goal: 01-NOV-2002

Brand Name : METHYLIN — (METHYLPHENIDATE HCL)ORAL SOL
Estab. Name:
Generic Name: METHYLPHENIDATE HCL ORAL SOLUTION 5MG/5M
Dosage Form: (LIQUID)
Strength : 5MG/5ML, 10MG/5ML

FDA Contacts: A. HOMONNAY WEIKEL Project Manager (HFD-120) 301-594-5535
C. JOHN Review Chemist (HFD-120) 301-594-2850
ID = 115238 Team Leader

Overall Recommendation: ACCEPTABLE on 12-NOV-2002by J. D AMBROGIO(HFD-324) 301-827-0062
ACCEPTABLE on 14-SEP-2001by S. FERGUSON(HFD-324) 301-827-0062

Establishment : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-NOV-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1317295 FEI : 1317295
MALLINCKRODT CHEMICAL INC
172 RAILROAD AVE, 58 PEARL, 18 CORNELL
HOBART, NY 13788

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-NOV-02
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BASED ON PROFILE

Establishment : CFN : 1940521 FEI : 1940521
MALLINCKRODT CHEMICAL INC
3600 NORTH 2ND ST
ST LOUIS, MO 63147

DMF No: 12769 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-NOV-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : [redacted]

DMF No:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-NOV-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : [redacted]

DMF No:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-NOV-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

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

/s/

Donald Klein
12/16/02 02:20:27 PM
CHEMIST

Stability evalution on p. 16 expanded; Related Substance A and B values bolded throughout the review.

Thomas Oliver
12/16/02 02:26:07 PM
CHEMIST