CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-475

CHEMISTRY REVIEW(S)

NDA 21-475

Methylin® CT
(Methylphenidate Hydrochloride Chewable Tablets)
2.5, 5.0 and 10 mg

Mallinckrodt Inc.

Xiao-Hong Chen, Ph.D.
Division of Neuropharmocological Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-475

2. REVIEW #2:

3. REVIEW DATE: March 31, 2003

4. REVIEWER: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA submission	December 19, 2001
Amendment BC	February 13, 2002
Amendment BC	August 29, 2002
Amendment BC	September 6, 2002
Amendment BL	September 10, 2002
Amendment BC	September 16, 2002
Amendment BC	September 24, 2002
Amendment BC	October 15, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AZ	February 14, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt, Inc.
Address:	675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134-0840
Representative:	Ronald T. Groman
Telephone:	(314) 654-6060

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Methylin® CT
b) Non-Proprietary Name (USAN): Methylphenidate Hydrochloride
c) Code Name/# N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Narcolepsy/sleep apnea

11. DOSAGE FORM: Chewable Tablets

12. STRENGTH/POTENCY: 2.5, 5 and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

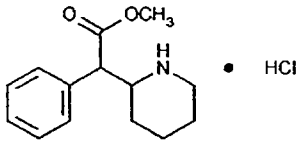
14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name	**Methylphenidate hydrochloride USP**
Chemical Name	Methyl α-phenyl-2-piperidineacetate hydrochloride
CAS number	298-59-9
Molecular Weight	269.77
Molecular Formula	$C_{14}H_{19}NO_2 \cdot HCl$
Structural formula	See above

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
	II	Mallinckrodt Inc.	Methylphenidate Hydrochloride USP	3	**Adequate**	5-1-2000	None
	IV			3	**Adequate**	9-15-2000	None
	IV			3	**Adequate**	4-29-2002	None
	IV			4	**Adequate**	10-15-2002	All Materials listed in 21CFR
	IV			3 3	**Adequate**	4-25-2002 8-13-1999	None
	IV			3	**Adequate**	4-29-2002	None
	IV			3	**Adequate**	1-24-1997	None

[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:

NDA 21-419	Methylin AQ (Methylphenidate HCl) Oral Solution	An approval letter was issued on 12/19/2002

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable (see Attachment)	15-Jul-02	Office of Compliance
Pharm/Tox	Pending		J Edward Fisher, Ph.D.
Biopharm	Acceptable	28-Aug-02	Wen-Hwei Chou, Ph.D.
Methods Validation	Pending		
DMETS	Acceptable	16-Oct-02	Alina Mohmud
EA	Acceptable – Categoricol exclusion granted	15-Oct-02	Xiao-Hong Chen, Ph.D.
Microbiology	Acceptable	25-Mar-03	John Metcalfe, Ph.D.

The Chemistry Review for NDA 21-475

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for **Approval**.

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

There are no Phase 4 commitments for this application.

II. Summary of Chemistry Assessments

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

Drug Product

Methylin®CT chewable tablets contain methylphenidate HCl, which is a mild central nervous system stimulant. Methylin®CT is manufactured as 2.5 mg, 5 mg, and 10 mg chewable tablets. The drug is used to treat deficit hyperactivity (ADHD) and narcolepsy (sudden attacks of uncontrollable sleepiness). The drug substance methylphenidate HCl USP has been used to manufacture several other FDA approved drugs such as Ritalin® methylphenidate hydrochloride USP tablets, Ritalin-SR® methylphenidate hydrochloride USP sustained-release tablets, Methylin® methylphenidate HCl tablets USP, Methylin® ER methylphenidate HCl extended-release tablets USP, etc. The applicant intends to market this dosage form as an alternative to Ritalin® tablets with equivalence dosing recommendations and for the labeled patient population. Methylin® CT 2.5 mg, 5 mg and 10 mg chewable tablets all contain the following inactive ingredients: aspartame NF, maltose, microcrystalline cellulose NF, and Guar Gum NF, pregelatinized starch NF, stearic acid NF, and [redacted] grape flavor. The drug product is manufactured by Mallinckrodt Inc. located in St. Louis, MO.

The drug product is manufactured [redacted] process — exhibit batches for each strength of the product (total —batches) have been manufactured. The master batch records for the commercial product and the executed batch records for the exhibit batches were provided.

The proposed regulatory specifications appear comparable to those of the similar marketed products. The applicant has agreed to tightened the specifications for [redacted] and unspecified impurities in the major amendment submitted on February 14, 2003.

The original test method employed a , which is now being replaced with a fell into a wide range with the method. The applicant conducted a study using another test apparatus and concluded that the variability was due to the used. The applicant proposed to replace the existing method with the new method, which reduced variation of test results. This method change also resulted in a change in the specification limits. The applicant was requested to conduct a study to demonstrate a The applicant has conducted this study and provided the data to support the proposed specifications. The revise appear acceptable and will be used for postapproval and stability testing.

The drug product stability studies were conducted using the ICH conditions. Each strength of the drug product is packaged into bottles with three different counts. The applicant has obtained up to stability data for lots of the Methylin Chewable Tablets. The drug product appears fairly stable under the long term storage conditions (24 months at 25°C/60%RH) and intermediate conditions at 30°C/60%RH). Most of the test data do not demonstrate a significant trend (increase or decrease), except the tests for impurity (from LT , at T_0 to at T_{24}), Total Impurities (from LT , at T_0 to at T_{24}) and Dissolution (from at T_0 to at T_{24}). However, all test results were within the specification limits. The stability testing was also being performed using the updated method, and data at are within the revised specifications (Attachment 2). The applicant requested 24 months expiry at 25°C and it is approved based on the stability data provided.

Drug Substance

Methylphenidate hydrochloride USP is a white, ordorless, fine crystalline powder. Methylphenidate HCl is a well-characterized drug substance. It has a chemical name of methyl α-phenyl-2- piperidineacetate hydrochloride. The molecular formula is $C_{14}H_{19}NO_2 \cdot HCl$ and the molecular weight is 269.77. Its solutions are acidic. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. The drug substance is manufactured by Mallinckrodt Inc. located in St. Louis, MO. The full details of the chemistry, manufacturing and controls for Methylphenidate Hydrochloride USP are provided in Mallinckrodt's Drug Master File

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

The drug is to be administered orally 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. Other patients may take 10 to 15 mg daily.

C. Basis for Approvability Recommendation

NDA 21-475 for Methylin® CT is recommended for **Approval** from CMC standpoint. All CMC deficiencies from review #1 have been satisfactorily addressed. The Office of Compliance has given an acceptable recommendation for all sites listed in the NDA.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Xiao Hong Chen, Ph.D. 31-Mar-03
ChemistryTeamLeaderName/Date: Thomas F. Oliver, Ph.D.
ProjectManagerName/Date: Anna M. Homonnay

C. CC Block

30 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

Xiao Hong Chen
4/8/03 04:39:40 PM
CHEMIST

Thomas Oliver
4/9/03 08:01:10 AM
CHEMIST

NDA 21-475

Methylin® CT
(Methylphenidate Hydrochloride Chewable Tablets)
2.5, 5.0 and 10 mg CII

Mallinckrodt Inc.

Xiao-Hong Chen, Ph.D.
HFD-150 Division of Oncology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-475

2. REVIEW #1:

3. REVIEW DATE: September 20, 2002

4. REVIEWER: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA submission	December 19, 2001
Amendment BC	February 13, 2002
Amendment BC	August 29, 2002
Amendment BC	September 6, 2002
Amendment BL	September 10, 2002
Amendment BC	September 16, 2002
Amendment BC	September 24, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Mallinckrodt, Inc.
Address:	675 McDonnell Blvd. P.O. Box 5840 St. Louis, MO 63134-0840
Representative:	Ronald T. Groman
Telephone:	(314) 654-6060

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Methylin® CT
b) Non-Proprietary Name (USAN): Methylphenidate Hydrochloride Chewable Tablets
c) Code Name/# N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Narcolepsy/sleep apnea

11. DOSAGE FORM: Chewable Tablets

12. STRENGTH/POTENCY: 2.5, 5 and 10 mg

13. ROUTE OF ADMINISTRATION: Oral

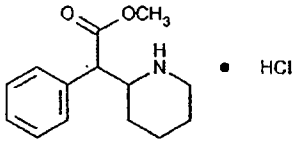
14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name	**Methylphenidate hydrochloride USP**
Chemical Name	Methyl α-phenyl-2-piperidineacetate hydrochloride
CAS number	298-59-9
Molecular Weight	269.77
Molecular Formula	$C_{14}H_{19}NO_2 \cdot HCl$
Structural formula	See above

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENT
	II	Mallinckrodt Inc.	Methylphenidate Hydrochloride USP	3	**Adequate**	5-1-2000	None
	IV			3	**Adequate**	9-15-2000	None
	IV			3	**Adequate**	4-29-2002	None
	IV			4	**N/A**		All Materials listed in 21CFR
	IV			3 3	**Adequate**	4-25-2002 8-13-1999	None
	IV			3	**Adequate**	4-29-2002	None
	IV			3	**Adequate**	1-24-1997	None

[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:

NDA	Methylin AQ (Methylphenidate HCl) Oral Solution	An approvable letter was issued on 5/31/2002

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical (efficacy)	Pending		Roberta Glass
EES	Pending (see Attachment)		
Pharm/Tox	Pending		J Edward Fisher
Biopharm	Acceptable	28-AUG-02	Wen-Hwei Chou
LNC	Pending		
Methods Validation	Pending		
OPDRA	Pending		
EA	Acceptable		
Microbiology	N/A		

The Chemistry Review for NDA 21-475

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is APPROVABLE. There are deficiencies related to drug product and labeling.

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

II. Summary of Chemistry Assessments

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

Drug Product

Methylin®CT chewable tablets contain methylphenidate HCl, which is a mild central nervous system stimulant. Methylin®CT is manufactured as 2.5 mg, 5 mg, and 10 mg chewable tablets. The drug is used to treat deficit hyperactivity (ADHD) and narcolepsy (sudden attacks of uncontrollable sleepiness). The drug substance methylphenidate HCl USP has been used to manufacture several other FDA approved drugs such as Ritalin® methylphenidate hydrochloride USP tablets, Ritalin-SR® methylphenidate hydrochloride USP sustained-release tablets, Methylin® methylphenidate HCl tablets USP, Methylin® ER methylphenidate HCl extended-release tablets USP, etc. The applicant intends to market this dosage form as an alternative to Ritalin® tablets with equivalence dosing recommendations and for the labeled patient population. Methylin® CT 2.5 mg, 5 mg and 10 mg chewable tablets all contain the following inactive ingredients: aspartame NF, maltose, microcrystalline cellulose NF, and Guar Gum NF, pregelatinized starch NF, stearic acid NF, and — grape flavor. The drug product is manufactured by Mallinckrodt Inc. located in St. Louis, MO.

The drug product is manufactured using — process. — exhibit batches for each strength of the product (total — batches) have been manufactured. The master batch records for the commercial product and the executed batch records for the exhibit batches are provided.

The proposed regulatory specifications appear comparable to those of the similar marketed products. However, acceptance criteria for the and unspecified impurities should to be tightened based on test data.

The original test method employed a which is now being replaced with a The sponsor discovered that the , while maintaining a consistent dissolution result ell into a wide range with the method. The applicant conducted a study using another test apparatus and concluded that the variability was due to used. The applicant proposed to replace the existing method with the new method. This method change also results in a change in the specification limits. However, no release or stability data are available for the product tested using the method. A commitment should be made by the applicant to provide test data and finalize specification (see section above). In addition, the sponsor has not demonstrated , and this information will be requested from the applicant.

The drug product stability studies were conducted using the ICH conditions. Each strength of the drug product is packaged into bottles with three different counts. The applicant did not use a bracketing design for the stability studies. The drug product with various strengths and different packaging configurations were all placed on long term, accelerated and intermediate stability. Up to primary stability data are provided. The drug product appears fairly stable under the long term storage conditions (25°C/60%RH). specified impurities, are present at the level of or less after storage at 25°C/60%RH. Levels of total impurities at under the long term storage conditions are also at or below. The sponsor will be asked to provide updated stability data to support their proposed expiry of 24 months.

Drug Substance

Methylphenidate hydrochloride USP is a white, ordorless, fine crystalline powder. Methylphenidate HCl is a well-characterized drug substance. It has a chemical name of methyl α-phenyl-2- piperidineacetate hydrochloride. The molecular formula is $C_{14}H_{19}NO_2 \cdot HCl$ and the molecular weight is 269.77. Its solutions are acidic. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. The drug substance is manufactured by Mallinckrodt Inc. located in St. Louis, MO. The full details of the chemistry, manufacturing and controls for Methylphenidate Hydrochloride USP are provided in Mallinckrodt's Drug Master File

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

The drug is to be administered orally 2 or 3 times daily, preferably 30 to 45 minutes before meals. Average dosage is 20 to 30 mg daily. Some patients may require 40 to 60 mg daily. Other patients may take 10 to 15 mg daily.

C. Basis for Approvability Recommendation

There are deficiencies in the drug product related to specifications and labeling. The overall recommendation for EES inspection is still pending. Based on the deficiencies and the pending EES recommendation, this application is approvable from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Xiao Hong Chen, Ph.D. 20-SEP-02
ChemistryTeamLeaderName/Date: Thomas F. Oliver, Ph.D.
ProjectManagerName/Date: Anna M. Homonnay

C. CC Block

43 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

Xiao Hong Chen
10/15/02 06:17:51 PM
CHEMIST

Thomas Oliver
10/15/02 06:23:05 PM
CHEMIST