CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-121

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 21-121 **CHEM REVIEW: #2** **REVIEW DATE: 7/15/00**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment(AZ)	6/1/00	6/5/00	6/7/00
Amendment(BZ)	6/14/00	6/15/00	6/22/00
Amendment(BC)	6/28/00	6/29/00	7/5/00
Amendment(BL)	7/7/00	7/10/00	7/11/00

NAME AND ADDRESS OF APPLICANT:
ALZA Corporation
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

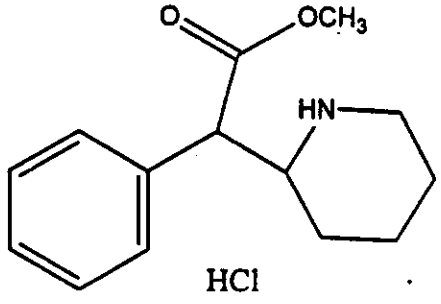
DRUG PRODUCT NAME:
Proprietary: CONCERTA™
Non proprietary/USAN: Methylphenidate hydrochloride
Code Name/Number: OROS®(methylphenidate HCl)
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Attention Deficit Disorder(ADD)/ Attention Deficit Hyperactivity Disorder(ADHD)

DOSAGE FORM: Osmotic Tablet
STRENGTHS: 18mg and 36mg
ROUTE OP ADMINISTRATION: Oral
DISPENSED: xx RX ___OTC

SPECIAL PRODUCTS: __Yes xx No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:
CA Name: 2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride, (R*,R*)-(±)-
USAN Name: Methylphenidate hydrochloride USP
Chemical Formula: $C_{14}H_{19}NO_2$. HCl
Molecular Weight: 269.77
CAS Registry Number: CAS-298-59-9
Laboratory code: None listed



Methods Validation *For FDA Lab*

[redacted]

RELATED REVIEW

Office of Clinical Pharmacology and Biopharmaceutics (M. Sunzel, Ph.D., I.Mahmood, Ph.D.) (M. Sunzel, Ph.D., P.Marroum, Ph.D.)	1st review completed 2/10/00 Addendum completed 4/17/00 Recommends: Revised dissolution specifications are Acceptable; Type A *in-vitro-in vivo* correlation is Acceptable.
Office of Post-Marketing Drug Risk Assessment (OPDRA, HFD-400; OPDRA Consult#: 99-021)	Submitted by HFD-120 under I54,575 on 7/29/99 Recommends: Concerta™ is Acceptable
ONDC, HFD-805(Micro.) (N. Sweeney, Ph.D.)	Submitted consult on 8/16/99(D.Klein), Recommends: Approval on 10/5/99.

COMMENTS:

1. [redacted]

d [redacted] ;%.

3. The proposed 24 month expiration date at 25°C for the 18mg and 36mg tablet in HDPE bottles is acceptable.
4. The stability commitments are acceptable.
5. The proposed Container Closure Change Protocol is acceptable.
6. ALZA has satisfactorily addressed the CMC deficiencies from the 5/18/00 Approvable letter.
7. The following CMC sections of the submission are **acceptable: Drug Substance specifications; Drug Product Components/Composition; Drug Product Manufacturer; Drug Product Manufacturing and Packaging; Drug Product Specifications; Drug Product Container Closure System; Drug Product Stability; Establishment Inspection; Package Insert and Labeling.**
8. [redacted]

CONCLUSIONS: Recommend Approval of the CMC section of N21-121. *Refer to the draft letter.*

/S/ 7/15/00
Donald N. Klein, Ph.D.
Review Chemist, HFD-120

/S/ 7/17/00
Robert H. Seevers, Ph.D.
Chemistry Team Leader, HFD-120

cc:
Orig. NDA 21-121
HFD-120/Division File
HFD-810/JSimmons
HFD-810/HPatel
HFD-120/DKlein
HFD-120/RSeevers
HFD-120/AMosholder
HFD-120/AMHomonnay
HFD-120/BRosloff
HFD-860/MSunzel
HFD-860/IMahmood
File: [redacted]

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 21-121 **CHEM REVIEW: #1** **REVIEW DATE:** 5/10/00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	7/15/99	7/19/99	7/21/99
AMENDMENT N(BC)	1/31/00	2/2/00	2/4/00
AMENDMENT N(SU)	2/15/00	2/16/00	2/17/00
AMENDMENT N(BZ)	3/29/00	3/30/00	4/5/00
AMENDMENT N(BC)	4/3/00	4/4/00	4/5/00
AMENDMENT N(BB)	4/4/00	4/5/00	4/10/00
AMENDMENT N(BC)	4/20/00	4/21/00	4/26/00

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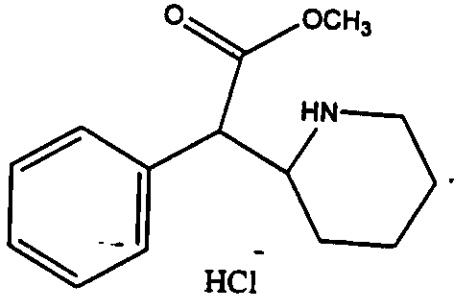

Methods Validation Pending

RELATED REVIEW

Office of Clinical Pharmacology and Biopharmaceutics (M. Sunzel, Ph.D., I.Mahmood, Ph.D.) (M. Sunzel, Ph.D., P.Marroum, Ph.D.)	1st review completed 2/10/00 Addendum completed 4/17/00 Recommends: Revised dissolution specifications are Acceptable; Type A *in-vitro-in vivo* correlation is Acceptable.
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ONDC, HFD-805(Micro.) (N. Sweeney, Ph.D.)	Submitted consult on 8/16/99(D.Klein), Recommends: Approval on 10/5/99.

COMMENTS:

1. The following CMC sections of the submission are **acceptable: Drug Product Specifications & Methods for Inactive Components; Drug Product Microbiology; Environmental Assessment; Investigational Formulation.**
2. The following CMC sections of the submission are **approvable: Drug Substance specifications proposed by ALZA; Drug Product Components/Composition; Drug Product Manufacturer; Drug Product Manufacturing and Packaging; Drug Product Specifications; Drug Product Container Closure System; Drug Product Stability; Establishment Inspection; Package Insert and Labeling.**

CONCLUSIONS: For the CMC section of the submission, I recommend **Approvable.** Refer to the list of deficiencies at the end of the review.

/S/ 5/10/00

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

/S/ 5/11/00

Robert Seevers, Ph.D.
Chemistry Team Leader, HFD-120

cc:
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HFD-120/AMHomonnay
HFD-120/BRosloff
HFD-860/MSunzel
HFD-860/IMahmood
File: [redacted]

APPEARS THIS WAY ON ORIGINAL