CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-121

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DF SEP 13 1998 [redacted]

CONSULTATION REQUEST/RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

5188

DATE SENT: September 10, 1999	**DUE DATE: N/A**	**OPDRA CONSULT #:** 99-021

TO (Division): Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
(HFD-120)

PRODUCT NAME: Concerta™ (Methylphenidate HCL) Extended-release Tablets **IND#:** [redacted]	**MANUFACTURER:** ALZA Corporation

CASE REPORT NUMBER(S): N/A

SUMMARY:

In response to the request by the Division of Neuropharmacological Drug Products, OPDRA conducted a review of the potential name confusion between the proposed proprietary name, "Concerta™", and other approved proprietary/generic names. This review is based on a study conducted within OPDRA with emphasis on the evaluation of the potential medication errors in handwriting and verbal communication of this proposed proprietary name.

OPDRA RECOMMENDATION:

OPDRA recommends that the proposed proprietary name, Concerta™, is acceptable. However, this name should be forwarded again to OPDRA within 60 days of NDA approval. This will assure that no newly approved FDA products are similar to this proposed proprietary name.

/S/ 9/3/99

y Phillips
ociate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3225
Fax: (301) 827-5189

/S/

Peter Honig, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

Evaluation of a proposed proprietary name "CONCERTA™"

DATE OF REVIEW: September 10, 1999

IND#: [redacted]

NAME OF DRUG: Concerta™ (Methylphenidate HCL)
Extended-release Tablets
18mg & 36mg

NDA HOLDER: ALZA Corporation

I. INTRODUCTION

This consult is in response to a request sent on July 29, 1999, from the Division of Neuropharmacological Drug Products and a request sent on April 8, 1999, from ALZA Corporation to review a proposed proprietary drug name, Concerta, and the alternative trade name, Concentra, regarding potential name confusion with existing proprietary/generic drug names.

This proposed drug product is indicated for the treatment of attention deficit hyperactivity disorder (ADHD). The proposed product will be available as 18 mg and 36 mg tablets. ALZA is seeking an approval for an oral once-a-day formulation.

This product was submitted under [redacted] ith the name [redacted] ALZA Corporation in conjunction with a market research firm [redacted] conducted seven focus group surveys of physicians and non-physicians (psychologists, pharmacists, and parents) in San Francisco and Chicago on the proposed tradename, Concerta, and the alternative name, Concentra. Fifty-seven respondents were asked to write the proposed tradename and were then asked to read the names into an audio tape recorder. Twelve pharmacists were then involved in prescribing and dispensing error test in which each pharmacist was to read and print the names as scripted by physicians, and to decipher the proposed names pronounced by the physicians in the audio recording. In written and discussion forums, all participants were asked to indicate if the proposed tradename or the alternative name reminded them of any existing drug products. No associations were made with other approved drug products for either name. Specifics of the study methodology was not provided and thus not evaluated by OPDRA.

II. RISK ASSESSMENT

Methylphenidate is a central nervous system stimulant, which could lead to serious adverse events when erroneously substituted for other drugs. Some of its known adverse events include tachycardia, hypertension, nervousness, precipitation of Tourette's syndrome, growth retardation, cardiac arrhythmia, and thrombocytopenia. In order to predict the potential medication errors and to determine the degree of confusion of this proposed proprietary name, Concerta, with other drug names, the medication error staff of OPDRA searched American Drug Index (42nd Edition), Drug Facts and Comparisons (1998 Edition), PDR (53rd Edition, 1999), Drug Product Reference File (DPRF), and EES (Established Evaluation System) for possible sound-alike or look-alike names to approved and unapproved drug products. In addition, OPDRA conducted a study of written and verbal analysis of the proposed proprietary name employing health practitioners within OPDRA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

Study conducted within OPDRA

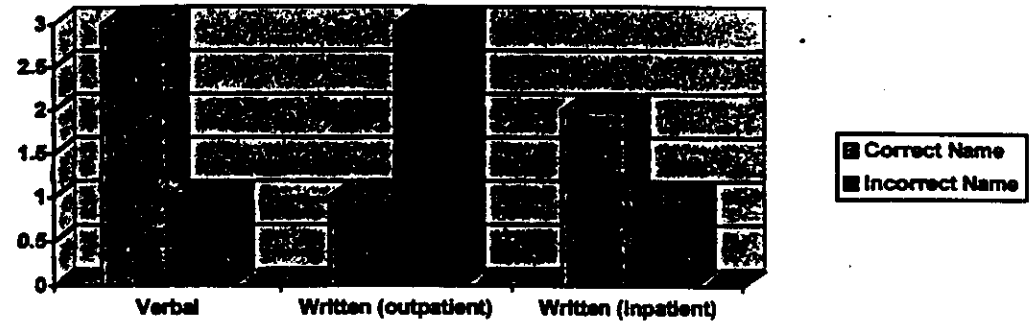
1) Methodology

This study involved 19 health professionals comprised of pharmacists, physicians, and nurses within OPDRA to determine the degree of confusion of Concerta and Concentra with other drug names due to the similarity in handwriting and verbal pronunciation of the name. For each proposed name, two OPDRA staff wrote one inpatient and one outpatient order. Each order consisted of two model prescriptions and a prescription for Concerta or Concentra. A random sample of the written orders, either inpatient or outpatient, was then delivered to the participating health professionals via e-mail. In addition, a volunteer physician with a foreign accent recorded a verbal order for three model prescriptions and a prescription for Concerta in a voice mail message. A pharmacist with an accent recorded a verbal order for Concentra. The voice mail messages were then sent to the participating health professionals for their review. After receiving either written or verbal orders, the participants sent their interpretations of the orders vial e-mail to the medication error staff. After receiving the interpretations of the orders, the correct spelling of the proposed proprietary name or the alternative name was sent to the health professionals with a request for handwriting samples of the names. The medication error staff then reviewed the samples of the handwritten names.

2) Results

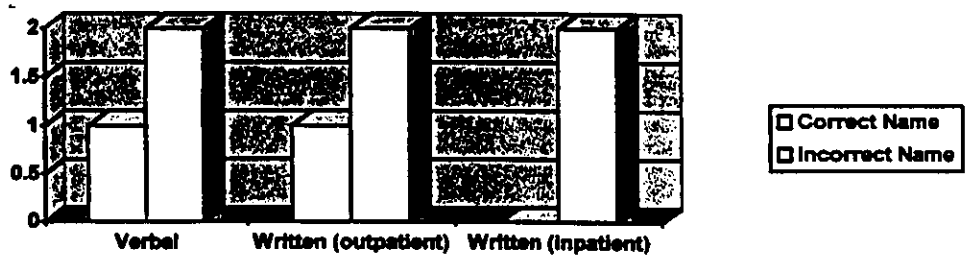
We received responses from sixteen participants, eight of which interpreted Concerta prescription orders and eight for Concentra orders. Three participants interpreted both written and verbal orders for Concerta. The interpretative responses and results are as follows:

Concerta



Incorrect names include: Concerto, Conectem, Coreento, Concuta, & Concesta

Concentra



Incorrect names include: Conctra, Consumptra, Corentra, Cogentin, & Canesatra

3) Analysis

The results of the verbal and written analysis studies demonstrate that six out of eleven replies by the participants interpreted the product name accurately for Concerta and two out of eight for Concentra. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name. However, in this case, the inaccurate interpretations of the proposed tradename, Concerta, did not overlap with any existing approved drug products. Moreover, the search in available texts, databases, and the handwriting samples did not produce any significam new information to render Concerta objectionable.

III. RECOMMENDATIONS

A. OPDRA has no objection to the use of the proprietary name, Concerta, for methylphenidate HCL extended-release tablets. However, we would request that you provide us with a follow-up consult 60 days before the expected approval date of the NDA.

B. OPDRA does not recommend the alternative name, Concentra. This proposed alternative name is very similar to existing proprietary drug names such as Concentraid, Concentrin, and Conceptrol. In addition, Concentra is close to "concentrated" and thus could imply that the product is concentrated, when in fact it is an extended-release formulation. This product is not a concentrated formulation.

C. We have reviewed the proposed container labels for clarity. OPDRA offers the following comments for the chemist to consider when the firm submits an NDA. We offer these comments only to minimize possible user error pertaining to the labeling.

1) The words, "Extended-release tablets", which appear under the established name seem to lose their prominence. We would encourage the manufacturer to increase that prominence. This information may be important since we don't want the user to believe that this is an immediate-release product.

2) The prominence and location of the Schedule II symbol need to be changed.

3) We would encourage consistency in nomenclature when describing the product. In particular, the side panel should be changed to reflect that this product is an "Extended-release formulation" and not a "Controlled-release formulation".

4) The net quantity appears rather small. We would encourage the manufacturer to increase its prominence.

If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301)827-3243.

/S/ 9/13/99

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 9/13/99

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

Office Files
HFD-120: Russell Katz, Director, Division of Neuropharmacological Drug Products
HFD-400: Jerry Phillips, Associate Director, OPDRA
HFD-400: Peter Honig, Deputy Director, OPDRA
HFD-2 : Mac Lumpkin, Acting Director, OPDRA

M E M O R A N D U M

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

DATE: July 29, 1999

FROM: Russell Katz, M.D., Acting Director 8/2/99
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Request for Assessment of a Trademark Review

TO: Jerry Phillips, R.Ph.
OPDRA
HFD-400/Pkln. Bldg. 15B23

Proposed Trademark: Concerta (methylphenidate HCl)

Established name, including dosage form: methylphenidate HCl controlled-release formulation/oral once daily

Other trademarks by the same firm for companion products:
none

Indications for use: Attention Deficit Disorder

Dosage regimen: once daily formulation

cc:
Orig IND
HFD-120
HFD-120/Seevers
HFD-120/Homonnay AHW

drafted by: ahw/7.29.99
C:-

Exclusivity Checklist

NDA: 21-121				
Trade Name: Concerta				
Generic Name: methylphenidate HCl Extended-release tablets				
Applicant Name: Alza Corp				
Division: HFD-120 Div of Neuropharm				
Project Manager:				
Approval Date: 1S				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" t one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	✓	No	
b. Is it an effectiveness supplement?	Yes		No	✓
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including you reasons for disagreeing with any arguments made by the applicant that the study was not simpl a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	✓	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	three			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously bee approved by FDA for the same use?	Yes		No	✓

If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	✓	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an alread approved active moiety.	Yes	✓	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product Ritalin Tablets				
NDA # 10-187				
Drug Product Ritalin SR Tablets				
NDA # 18-029				
Drug Product				
NDA #				
2. Combination product.	Yes		No	✓
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed unde an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				

NDA #	
Drug Product	
NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed onl if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (Th Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	✓	No	

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is n essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical tria such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from so other source, including the published literature) necessary to support approval of the application or supplement?	Yes	✓	No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approva **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:
New PK profile of formulation requires a clinical study

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	✓
1) If the answer to 2 b) is "yes," do you personally know of an reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	✓

If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: C-97-025				
Investigation #2, Study #: C-98-003				
Investigation #3, Study #: C-98-005				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been reli on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by th agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approv application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	✓
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	✓
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application				

or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any th are not "new"):

Investigation #1	
Investigation #2	
Investigation #3	

4. To be eligible for exclusivity, a new investigation that is essential to approval must also hav been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 C-97-025	Yes	✓	No	
IND#: —				
Explain:				
Investigation #2 C-98-003	Yes	✓	No	
IND#: —				
Explain:				
Investigation #3 C-98-005	Yes	✓	No	
IND#: —				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interes provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				

Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there othe reasons to believe that the applicant should not be credited with havin "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

BACK TO TOP

Signature of PM/CSO
Date:
Signature of Division Directo
Date:
cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

BACK TO TOP

SECTION 13. PATENT DECLARATON

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of OROS® (methylphenidate HCl). This product is the subject of this application for which approval is being sought.

PATENT NO.	TYPE	EXPIRATION	PATENT OWNER
5,082,668	Formulation	09/16/2003	ALZA Corporation
4,783,337	Formulation and Method of Use	09/16/2003	ALZA Corporation
4,612,008	Formulation	09/16/2003	ALZA Corporation
4,519,801	Formulation	07/12/2002	ALZA Corporation

Peter D. Staple
Senior Vice President and General Counsel
Dated: May 26, 1999

SECTION 13. PATENT DECLARATION

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4,612,008	Formulation	09/16/2003	ALZA Corporation
4,519,801	Formulation	07/12/2002	ALZA Corporation
4,327,725	Formulation	11/25/2000	ALZA Corporation

Peter D. Staple
Senior Vice President and General Counsel
Dated:

July 15, 1999

NDA 21-121
Volumes 1.1 – 1.209

Food and Drug Administration; CDER/ODE I
Division of Neuropharmacological Drug Products (DNDP/HFD-120)
Attention: Document Control Room
1451 Rockville Pike
Rockville, MD 20852

Attention: Russell Katz, MD, Acting Director, DNDP

Subject: Submission of Original New Drug Application (NDA) 21-121 for OROS® (methylphenidate HCl) Extended-release Tablets

Dear Dr. Katz:

In accordance with Section 505(v) of the Federal Food, Drug, and Cosmetic Act, and with the provisions of 21 CFR 314.50, ALZA Corporation (ALZA) hereby submits an NDA for OROS® (methylphenidate HCl) Extended-release Tablets, a once-daily controlled release formulation of methylphenidate HCl.

Please find detailed information regarding the content and organization of the NDA in Section 1 of the application. Because ALZA has conducted significant new clinical investigations that are essential to approval of this application, we are requesting exclusivity under 21 CFR Section 314.108.

ALZA appreciates the Division's guidance on the development of this new product and we look forward to our continued interactions as the review of this application proceeds. Please feel free to contact me with any questions or comments at 650-962-4282, or via facsimile at 650-237-2581. In the event that you are unable to reach me, please contact either Jennifer Ekelund, Senior Regulatory Affairs Associate, at 650-237-2543 or Dr. Steve Ketchum, Director of Regulatory Affairs, at 650-237-2510. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

ALZA CORPORATION 950 PAGE MILL ROAD P.O. BOX 10950 PALO ALTO CA 94303-0802 PHONE 650.494.5000 http://www.alza.com

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21121	**Trade Name:**	OROS (METHYLPHENIDATE HCL) 18MG/36MG TABS
Supplement Number:		**Generic Name:**	METHYLPHENIDATE HCL
Supplement Type:		**Dosage Form:**	Tablet, Extended Release; Oral
Regulatory Action:	AE	**Proposed Indication:**	attention deficit disorder

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
_X_ Other Age Groups (listed): 6 - 13 years
____Children (25 Months-12 years)
____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANNA MARIE HOMONNAY-WEIKEL

Signature /S/ _____ Date 4/19/00

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 29, 2000

TO: Anna Marie Homonnay, R. Ph., Regulatory Project Manager
Andrew Mosholder, M.D., Clinical Reviewer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-121

APPLICANT: ALZA Corporation

DRUG: Oros (methylphenidate hydrochloride) 18 mg/36 mg Tablets

CHEMICAL CLASSIFICATION: Type 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder

CONSULTATION REQUEST DATE: August 27, 1999

ACTION GOAL DATE: May 19, 2000

I. BACKGROUND:

Oros (methylphenidate hydrochloride) is a CNS stimulant, formulated as a once-a-day controlled-delivery methylphenidate drug product for the treatment of Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder.

Inspection assignments that were issued covered three clinical investigational sites and three protocols, as noted below. The goals of the inspections were to validate the data submitted by these sites in support of pending NDA 21-121.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Pelham	Buffalo	NY	10-06-99	01-22-00	NAI
Swanson & Wigal	Irvine	CA	10-06-99	12-06-99	VAI
Biederman	Boston	MA	10-06-99	01-10-00	VAI

A. Protocol #C-97-025

1. William E. Pelham, Jr., Ph.D.

This site enrolled seventy (70) subjects, sixty-eight (68) of whom completed the study. Two subjects (#29039 and #29067) were terminated at the sponsor's request because parents dosed the subjects with non-study drug during the C-97-025 trial.

Records for fifteen (15) subjects were reviewed. This review covered comparison of source data with case report forms, informed consent, subject birthdates, primary endpoint data, adverse events, concomitant medications, and drug disposition. No significant deviations from federal regulations or GCPs were noted.

B. Protocol #C-98-003

1. James Swanson, Ph.D., and Sharon Wigal, Ph.D.

This site enrolled sixty-four (64) subjects, sixty-one (61) of whom completed the study. Three (3) subjects were withdrawn from the study by their parents/guardians: Subject #19200, withdrawn due to parent/guardian apprehension; subject #19168, withdrawn due to parent/guardian preference to return subject to pre-study Ritalin and clonidine; and subject #19224, withdrawn by parent/guardian because of rash.

Records for twelve (12) subjects were reviewed, including history and physical examination forms; ADHD diagnostic reports (DISC and DSM-IV); parent and teacher assessment forms; progress notes written by physicians, teachers and study coordinators; and hematology, blood chemistry, and urinalysis laboratory reports.

The following deviations were noted:

(a) Study-termination laboratory testing was not done for any of the subjects; however, subjects from this study were reportedly enrolled into a second, related study in which laboratory testing was done for safety purposes.
(b) Study-termination physical examinations were not documented for the twelve subjects whose records were audited.
(c) Several adverse events were not reported, none of which were considered serious.

It is felt that the foregoing deviations do not impact the acceptability of the data from this site.

C. Protocol #C-98-005

1. William E. Pelham, Jr., Ph.D.

This site enrolled twenty-eight (28) subjects, twenty-six (26) of whom completed the study. Two subjects (#29117 and #29107) withdrew because consent was withdrawn by their parents.

Records for six (6) subjects were reviewed. This review covered comparison of source data with case report forms, informed consent, subject birthdates, primary endpoint data, adverse events, concomitant medications, and drug disposition. No significant deviations from federal regulations or GCPs were noted.

2. James Swanson, Ph.D., and Sharon Wigal, Ph.D.

This site enrolled twenty-six (26) subjects. Four (4) subjects were discontinued: Subject #19241 was unable to swallow capsule; subjects #19195 and 19225 discontinued because of lack of efficacy; and subject #19237 discontinued because of an adverse event related to study treatment but not further specified in the inspection report.

Records for twelve (12) subjects were reviewed, including history and physical examination forms, ADHD diagnostic reports (DISC and DSM-IV), parent and teacher assessment forms, and progress notes written by physicians, teachers and study coordinators. No significant deviations from federal regulations or GCPs were noted.

3. Joseph Biederman, M.D.

Twenty-four (24) subjects were enrolled at this site; sixteen (16) completed the study; eight (8) were terminated, with reasons including lack of efficacy, mood alteration (irritability), non-compliance and loss to follow-up. No deaths or serious adverse experiences were reported. There were inadequate drug accountability records at this site, but this issue has been satisfactorily responded to by the clinical investigator.

Records for twelve (12) subjects were reviewed. No significant deviations from federal regulations or GCPs were noted.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Although there were deviations noted in the conduct of protocol #C-98-003 by Drs. Swanson and Wigal, which are outlined above, the data from all sites appear acceptable for use in support of the pending NDA.

Key to Classifications:

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
VAIr = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable
Pending = Inspection not completed

/S/

Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

/S/

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-121
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Hajarian
HFD-47/GCP II Branch Chief
HFD-47/Lewin
HFD-45/Kline for GCPB Files #2881, #9960 and #9918
HFD-45/Reading File

Request for Audit

DATE: August 27, 1999

8-27-99 JPL

FROM: Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Study-Oriented Audits for NDA

TO: DSI Staff: Mathew Thomas, M.D.

Please refer to the attached August 20, 1999, correspondence to Dr. Burnett, from Alza Corporation regarding pending NDA 21-121 for OROS^{R} (methylphenidate hydrochloride) Extended-release Tablets for the treatment of attention deficit disorder in children.

Please audit any sites as necessary. The 10 month goal date of this application is 5/21/00. If you should have any questions, please contact: Ms. Anna M. Homonnay-Weikel, R.Ph., Regulatory Project Manager at (301) 594-5535.

C:\WPFILES

HFD-120

Homonay

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 24 2000

William E. Pelham, Jr., Ph.D.
Professor of Psychology
State University of New York at Buffalo
Department of Psychology
Park Hall
Buffalo, New York 14260-4110

Dear Dr. Pelham:

Between November 22 and December 9, 1999, Ms. Kim M. Downing, representing the Food and Drug Administration (FDA), met with you and members of your staff to review your conduct of two clinical studies (protocols C-97-025 and C-98-005) of the investigational drug Oros (methylphenidate hydrochloride), performed for ALZA Corporation. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and data listings provided by the sponsor, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Downing during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

FEI: #3002829015
Field Classification: NAI
Headquarters Classification: NAI
__X__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:

Deficiencies noted: None
____inadequate informed consent
____inadequate drug accountability
____failure to adhere to protocol
____inadequate records
____failure to report ADRS ____
____other

cc:
HFA-224
HFC-230
HFD-120/Review Div. Dir.
HFD-120/MO/Mosholder
HFD-120/PM/Homonnay
HFD-120/Doc. Rm. NDA #21-121
HFD-45 r/f
HFD-47 c/r/s GCP file #09960
HFD-47 Lewin/Hajarian
HFR-NE150/Woyshner
HFR-NE350/DIB/Thomas
HFR-NE350/BIMO Monitor/Podsadowski
HFR-NE3500/Field Investigator/Downing

r/d:cl/2-21-00
reviewed:AEH:**(2/22/00)**
f/t:mb:**(2/22/00)**

Note to Rev. Div. M.O.

Protocol #C-97-025:

This site enrolled seventy (70) subjects, sixty-eight (68) of whom completed the study. Two subjects (#29039 and #29067) were terminated at the sponsor's request because parents dosed the subjects with non-study drug during the C-97-025 trial.

Records for fifteen (15) subjects were reviewed. This review covered comparison of source data with case report forms, informed consent, subject birthdates, primary endpoint data, adverse events, concomitant medications, and drug disposition.

Data appear acceptable.

Protocol #C-98-005:

This site enrolled twenty-eight (28) subjects, twenty-six (26) of whom completed the study. Two subjects (#29117 and #29107) withdrew because consent was withdrawn by their parents.

Records for six (6) subjects were reviewed. This review covered comparison of source data with case report forms, informed consent, subject birthdates, primary endpoint data, adverse events, concomitant medications, and drug disposition.

Data appear acceptable.

MEMORANDUM

DATE: July 31, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-121

SUBJECT: Action Memo for NDA 21-121, for the use of OROS Methylphenidate for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

The NDA for CONCERTA (OROS methylphenidate) as a once a day dosage formulation was submitted by Alza Corporation on 7/15/99, and was the subject of an Approvable letter dated 5/18/00. In that letter, the sponsor was asked to adopt specific dissolution specifications, commit to conduct a Phase 4 study to examine the effects of methylphenidate on developing systems in animals, and respond to multiple CMC issues. In addition, of course, the Approvable letter was accompanied by draft labeling which we asked the sponsor to adopt.

The sponsor responded to the Approvable letter in a submission dated 6/1/00. This submission has been reviewed by Dr. Andrew Mosholder, medical officer (review dated 7/11/00), Dr. Barry Rosloff, pharmacologist (comments dated 5/22/00 and 7/5/00), Dr. Donald N. Klein, chemist (review dated 7/15/00), Dr. Maria Sunzel, biopharmaceutics (review dated 6/12/00), and Dr. Tom Laughren, Psychiatric Drugs Team Leader (comprehensive memo dated 7/15/00).

All reviewers recommend that the application be approved.

The sponsor has addressed the CMC, pharmacology, and biopharmaceutics issues satisfactorily. I have only a few comments related to some clinical issues.

In his review, Dr. Mosholder notes that the cut-off date for the Safety Update submitted in the sponsor's resubmission was 5/18/00, but notes that there was considerable safety information not reported to the application (for example, he states on page 2 that there were large numbers of patients in study C-98-012 who dropped out, without explanation, before completing the 12 months of this study, and that no data was provided for patients continuing in the second 12 month extension of this study). I have discussed this with him, and he has confirmed that all serious adverse events and discontinuations due to adverse events that occurred up to the cut-off date of 5/18/00 have been described in the re-submission. He further notes that no new important adverse event information has emerged from this updated experience. For this reason, I believe that the safety experience has been adequately described, and that there is nothing in the safety database that would preclude approval.

There is one final issue.

In the draft labeling accompanying the Approvable letter, we proposed that the use of this product in patients with potentially constricted GI tracts be contraindicated, given that we believed that the product did not appreciably change in shape or consistency as it passed through the GI tract. Dr. Laughren now feels that its use in this population need not be contraindicated, but Dr. Mosholder still believes it should be.

Upon reconsideration, I believe that inclusion of this language as a Contraindication is probably not necessary at this time, because 1) there is no affirmative evidence that there has been a problem of the sort we are concerned about with this particular product, and 2) I can envision patients with one of these conditions possibly needing treatment with this product.

On the other hand, I still believe that its use in this sub-group should ordinarily be avoided. While we have no affirmative evidence that this product poses a threat of obstruction in these compromised patients, it is fair to say that we also have no experience (or very little) in this group of patients. Further, products of this type have been associated with (apparently rare) episodes of obstruction in patients with compromised GI tracts, and 1) this product is larger than most of these other products, and 2) the population which is likely to be prescribed this particular product will include many children, who are likely to be at greater risk than adults for obstruction if they have intestinal disorders.

We have discussed these matters with the sponsor in a phone conversation on 7/31/00. They have informed us that, while the product does retain its shape during GI transit, it does not retain its original "hardness", but that it acquires the density of water, making it considerably softer than the unswallowed tablet. Based on these considerations, we have agreed that there will be a statement in the Warnings Section describing the potential risk, and stating that this product should ordinarily not be administered to patients with compromised GI tracts.

As Dr. Laughren notes in his memo, all other labeling issues have been resolved. In particular, the sponsor's arguments have not been convincing regarding the inclusion of the duration of effect of the treatment as measured by a subscale of the SKAMP.

For these reasons, I will issue the attached Approval letter with accompanying labeling.

/S/

Russell Katz, M.D.

Cc:
NDA 21-121
HFD-120
HFD-120/Katz/Laughren/Mosholder/Homonnay/Rosloff/Fitzgerald
HFD-120/Klein/Seevers
HFD-860/Sunzel

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: May 18, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-121

SUBJECT: Action memo for NDA 21-121, for the use of Concerta (methylphenidate HCl) Extended-release Tablets

NDA 21-121, for the use of extended release methylphenidate (OROS) in patients with attention deficit hyperactivity disorder (ADHD), was submitted by Alza Corporation on 7/15/99. The application contains the results of 3 randomized controlled trials (2 cross-over studies and one parallel group study in which patients were randomized to OROS once a day, Ritalin three times/day, or placebo) which establish the effectiveness of the treatment for this indication. In addition, the sponsor has submitted safety data in over 700 subjects, which establish that the treatment can be given safely with appropriate labeling, given the experience with the long marketed immediate release methylphenidate products.

The application has been reviewed by Dr. Klein, chemist (reviews dated 4/12/00, 4/29/00, and 5/10/00), Drs. Mahmood and Sunzel, Office of Clinical Pharmacology and Biopharmaceutics (review dated 2/10/00), Dr. Shen, statistician (review dated 4/7/00), Dr. Rosloff, pharmacologist (review dated 4/12/00), Dr. Mosholder, medical reviewer (review dated 3/23/00), Dr. Joseph, medical reviewer, Division of Gastrointestinal and Coagulation Drug Products (review dated 3/2/00), Dr. Sweeney, Office of New Drug Chemistry, Microbiology staff (review dated 10/5/99), and Dr. Michael Klein, Division of Anesthetic, Critical Care, and Addiction Drug Products (review dated 1/6/00). Dr. Tom Laughren, Psychiatry Drugs Team Leader, has performed a comprehensive review (memo dated 4/27/00). The team recommends that the application be considered Approvable with the attached draft labeling.

The sponsor has proposed that information relating to the time course of effect of the OROS and the effect of the OROS formulation relative to the immediate release Ritalin be included in labeling. Both Drs. Mosholder and Laughren object to the inclusion of this information, primarily because these outcomes were not primary outcomes, and represent a subset of secondary outcomes.

With regard to the sponsor's proposal to include the time course of effect, in the 2 cross-over trials, the data show that for hours 2-12 post-dose (see Dr. Mosholder's review, pages 13 and 16), both OROS and Ritalin clearly separate from placebo on the SKAMP. However, Dr. Mosholder points out that we have

no data regarding the sensitivity of the SKAMP to detect a loss of effect; the inclusion of a single dose of immediate release methylphenidate would have been useful as a measure of assay sensitivity for this measure.

I take the points made by Drs. Laughren and Mosholder, and agree with the general principle that secondary outcomes should ordinarily not be described in labeling. Although this outcome was apparently considered an "important" secondary outcome in the protocols, and the finding appears robust within and across studies by the sponsor's analyses (which are based on averaging scores for all 3 periods), there are inconsistencies in the response on this outcome by period (see Dr. Shen's review, page 11 and 18; in one study, there was little effect in Period 1, while in the other study, the largest effect was in Period 1). I would, however, consider the inclusion in labeling of this information as description (perhaps presented, for example, without p-values) if the sponsor could adequately justify its inclusion, including justifying the use of this particular subset of the SKAMP for the purpose of measuring time course of effect, addressing the period effect seen, and addressing Dr. Mosholder's point.

With regard to the sponsor's desire to include in labeling information suggesting that the effects of OROS are comparable to those of Ritalin, Dr. Laughren notes that the sponsor apparently chose (without Agency agreement) as an upper limit for the confidence interval for the difference between treatments 1.2 points on the primary rating scale as being clinically meaningful. This raises the question of the appropriateness of this design to establish non-inferiority of the OROS compared to the immediate release product.

Further, in these trials, all patients had been receiving methylphenidate treatment prior to enrollment, and were switched to a dose of immediate release methylphenidate of either 5, 10, or 15 mg TID, depending upon their pre-study dose and regimen, which could have been considerably different than their assigned study dose. Given this, we cannot say with any assurance that patients were treated with optimal Ritalin doses in the trials, and it is therefore difficult to make fair comparisons of the effect of OROS and Ritalin. For these reasons, then, I agree that language in labeling explicitly stating or implying the equivalence of the 2 is not sufficiently supported by the evidence, and should not be permitted.

The one additional potential safety issue that requires consideration is the use of the OROS dosage form in small children. While other OROS products have been used in the pediatric population and have been well tolerated (with serious adverse events largely limited to those patients with intestinal conditions that predispose to obstruction), this particular tablet is the largest one used to date, and therefore raises the possibility that obstruction might be a greater problem. I believe that this is an issue of concern, and the draft labeling that the review team has drafted includes appropriate language addressing this issue.

For the reasons cited above, I will issue the attached Approvable letter with draft labeling.

/S/

Russell Katz, M.D.

Cc:
NDA 21-121
HFD-120
HFD-120/Laughren/Mosholder/Homonnay-Weikel/Fitzgerald/Rosloff
Seevers/Klein/Katz
HFD-860/Mahmood/Sunzel
HFD-710/Shen/Jin

M E M O R A N D U M

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

DATE: July 15, 2000

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

SUBJECT: Recommendation for Approval Action for
Concerta (OROS methylphenidate) for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

TO: File NDA 21-121
[**Note:** This overview should be filed with the 6-1-00 response to our 5-18-00 approvable letter.]

Background

In our 5-18-00 approvable letter, we proposed draft labeling, and we asked for a safety update, a regulatory status update, a world literature update, the adoption of our proposed dissolution specifications, and a commitment to conduct a phase 4 preclinical study on the effects of methylphenidate on developing systems. Finally, we conveyed a number of CMC questions and comments.

The sponsor responded with a 6-1-00 package that responded to all of these issues.

Safety Update

The cutoff date for the previous safety update was 10-31-99. This final safety update included safety data from 3 studies (C-98-012, C-99-025, and C-99-018), and had a cutoff date of 5-18-00. The bulk of the new safety experience came from study C-99-018, an open label study involving approximately 1100 patients. Dr. Mosholder reviewed these data, and concluded that there were no new safety findings that would impact on the approvability or labeling of this product. I agree.

Regulatory Status Update

To my knowledge, this product has not been submitted to any regulatory agency other than FDA.

World Literature Update

No new information was discovered in the updated literature search.

Dissolution Specifications

The sponsor accepted our proposed dissolution specifications.

Preclinical Study

The sponsor agreed to submit a draft protocol for a juvenile animal study within 90 days of the approval of this product.

CMC Deficiencies

To my knowledge, all remaining CMC issues have been resolved.

Pediatric Waiver

In the original application, Alza had requested a waiver from studying Concerta in children under the age of 6. Given the relatively large size of this capsule, it is not, in my view, feasible or necessary to study Concerta in younger children, and I recommend that we waive this requirement. Thus, the labeling will have the standard methylphenidate language in Warnings indicating that it should not be used in children younger than 6.

Labeling

We had a teleconference with Alza regarding labeling on 5-26-00, even before submission of the response to the approvable letter, to discuss labeling issues. A number of issues were discussed, but it appeared that the major concerns involved (1) the handling of language regarding the potential for GI obstruction, and (2) how best to describe and characterize the clinical benefits Concerta, in particular regarding duration of action over the course of a day. We subsequently had a telconference with Alza on 6-19-00 to specifically discuss again the issue of a potential for GI obstruction and a final labeling telcon with Alza on 7-7-00 during which we reached agreement on labeling, at least at the Team Leader level.

<u>Characterizing the Clinical Benefits of Concerta in Labeling</u>

There was no controversy about the primary outcome for the 3 studies, which was the Inattention/Overactivity subscale of the Iowa Conners Rating Scale. Alza also wanted to be able to characterize Concerta as having activity over the course of a 12 hour day based on SKAMP findings from the 2 laboratory classroom studies, 003 and 025. The major question was whether or not the protocols for these studies had planned the analyses for these studies in such a manner as to support

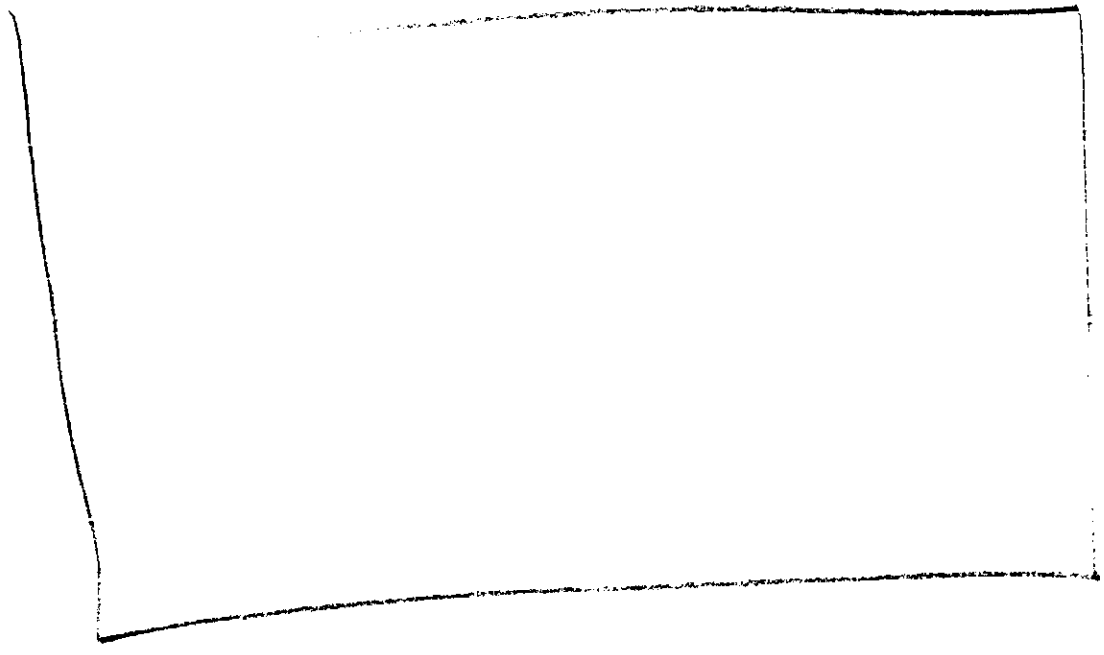
the inclusion of these findings in labeling. In the 5-26-00 telcon and in the 6-1-00 response, Alza made the case that the SKAMP combined attention assessements had been identified as the secondary outcome of greatest interest, and the stepwise analyses of these data, beginning with hour 1 after dosing and ending with hour 12 after dosing, had been adequately specified in the protocols in order to protect the overall alpha for the studies. In fact, the protocols did specify conditional stepwise testing of these outcomes, i.e., the studies would have to be positive initially on the Conners, and only then could testing of the SKAMP data proceed, with stepwise testing at each time point (0.05 for each such test, with testing proceeding to the next time point only if the previous time point was positive). After several internal discussions with biometrics and clinical staff, we reached agreement that this approach was acceptable. However, there was one additional problem. Period effects for the SKAMP findings were apparent in both studies, with different results in the 2 studies. For study 003, drug effect was minimal in period 1, but much stronger in periods 2 and 3. For study 025, period 1 had the strongest drug effect, with somewhat weaker results in periods 2 and 3. The sponsor's analyses were based on the averaging of effects across all 3 periods in each study, which resulted in a masking of the period effects and highly significant p-values at all time points from hour 2 on, in both studies (see my 4-27-00 memo). The impact of the differences across periods was to give different estimates of onset time and duration of effect after onset of effect. [Note: Onset was defined in the protocol as the time point half-way between the time at which no effect was observed and the time point at which an effect was first observed. Offset was defined as the time point half-way between the last time at which an effect was observed and first time point at which no effect was observed. Duration of effect would then be the difference between onset and offset of effect.] After much internal discussion, we decided that the most reasonable resolution would be to characterize onset and offset ranges for the periods in these studies, resulting in estimates for onset time of 1.5 to 4 hours, and estimates of duration from 8 to 11 hours. We proposed these estimates to the sponsor and further discussed this matter on 7-7-00. While there was much discussion of this issue, we could not reach agreement on how to convey the data from these studies into labeling. Alza felt that they had adequately addressed the period problem (by averaging), however, we disagreed. The difficulty is that there is no standard approach to dealing with period effect in a study like this with multiple timepoints. They argued that we were not taking baseline into account, however, they weren't either (simply averaging to increase sample size). The bottom line is that the results are very different by period, and admittedly don't make sense for IR either; we acknowledged that our proposed labeling was the best we could do to salvage these data, and admittedly not ideal. In the end, we agreed not to agree, and they accepted not mentioning the results of SKAMP data at all in labeling. In the future, they may try another analysis to convince us that these data speak to onset and duration. Thus, all references to SKAMP data, onset time, duration, etc, have been removed from labeling. While the SKAMP data are not mentioned in labeling, the labeling is clear in indicating the Concerta is effective when given once qd, and this dosing advice implies a sustained effect, thus, it seems to me, accomplishing the sponsor's goal.

Alerting Clinicians to a Potential for GI Obstruction with Concerta

In the version of labeling accompanying the approvable letter, we had proposed a Contraindication of Concerta use in children having certain GI disorders that might predispose to obstruction. This

was based on the advice of Dr. Ray Joseph from HFD-580. His initial argument was based on the relatively large size of this capsule, the rare reporting of cases of GI obstruction in adults with other OROS formulations, and a theory that children, due to their smaller size, may be more likely to develop GI obstruction. In their 6-1-00 response, Alza argued that a Contraindication for this product is inconsistent with the labeling for all other OROS products, all of which have a Precautions statement. They also argued that it is equally plausible, but admittedly speculative, that children because of their younger age and generally more robust physiological state may actually have a better ability to pass foreign objects than the older adults for whom obstruction has rarely been reported for these products.

We (including Judy Racoosin, M.D., the Safety Group Team Leader) met with Dr. Joseph on 7-6-00 and discussed these various arguments. He acknowleged that his recommendation for a Contraindication was based entirely on a theoretical argument that the problem might be worse in children, and that (1) the relative preponderance of cases with nifedipine could be related to the pharmacological effects of that drug on the smooth muscle of the GI tract, and (2) there was no evidence to suggest that the different sizes of the existing OROS products was a factor in the frequency of reported cases. There was general agreement that a Precautions statement listing the various conditions for which particular caution would be indicated would suffice. In addition, we agreed that the sponsor should be requested in the approval letter to report any cases suggestive of GI obstruction as 15-day reports. Dr. Josesph later suggested the terms "GI obstruction (esophagus through colon)" and "GI perforation" for use in this expedited reporting. Dr. Mosholder added the term "bezoar."



-Finally, I feel that requiring expedited reporting for any such events will ensure that, if the problem occurs, it will be detected.
-Thus, I have forwarded labeling that includes a Precautions statement rather than a Contraindication regarding this potential adverse event.

Recommendations

I believe that Alza has submitted sufficient data to support the conclusion that Concerta capsules are effective and acceptably safe in the treatment of ADHD. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling that is attached to the approval package.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA 21-121
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/AHomonnay

MEMORANDUM

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

DATE: April 27, 2000

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

SUBJECT: Recommendation for Approvable Action for
Concerta (OROS methylphenidate) for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

TO: File NDA 21-121
[**Note:** This overview should be filed with the 7-15-99 original submission.]

1.0 BACKGROUND

Methylphenidate is a stimulant that has been available for many years in the US as a treatment for ADHD, both in an immediate release form (Ritalin) and in a sustained release form (Ritalin SR). Immediate release methylphenidate is rapidly cleared and needs to be given at least twice and often even three times a day. The necessity of giving methylphenidate at lunchtime in a typical school setting is considered a major disadvantage to the immediate release form. While Ritalin SR should theoretically preclude the need for multiple daily administrations, in practice this formulation has been viewed as less effective than immediate release methylphenidate given on a divided schedule. While it is not well understood why this is so, one view is that tolerance to the beneficial effects may occur as a result of a constant input. The OROS methylphenidate formulation is intended to partly mimic immediate release administration by providing an initial bolus in the morning (by dissolution of the drug overcoat). and then possibly exceed the benefits of a second immediate release dose at lunchtime by providing an increasing plasma methylphenidate concentration over the remainder of the day (by osmotic delivery of the core drug on the basis of an osmotic gradient) . This impression is based on "sipping studies" comparing various input curves for methylphenidate. However, its major advantage would presumably be its effectiveness with only am dosing.

Other immediate release stimulant products approved for ADHD include various amphetamines (d-amphetamine, a mixture of d- and l-amphetamine, and methamphetamine) and pemoline. D-amphetamine is also available in a sustained release formulation.

[redacted] methylphenidate was originally submitted 11-14-97.

An EOP2 meeting was held with the sponsor on 8-20-98. Since a methylphenidate immediate release (IR) arm was included in the key clinical studies, the question was raised regarding whether or not comparative claims vs the IR formulation were planned. We suggested that the currently planned studies may not be adequate for such a claim. This caution was clearly articulated in our minutes of that meeting, and the sponsor's minutes noted that no comparative claims were planned. However, in 1-8-99 correspondence, the sponsor proposed a plan for claiming equivalence between the OROS methylphenidate and IR formulations, both in overall efficacy and in effectiveness over a 12-hour day . In a 2-24-99 letter we raised a number of objections to their plan, including the facts that they had not identified equivalence with IR methylphenidate as a primary outcome and that they had selected the IOWA Conners Teachers Rating Scale (Inattention/Overactivity subscale) as the primary outcome for their 3 clinical studies, a measure not necessarily well-suited for comparing time course for the OROS methylphenidate and the IR. We also raised other objections (see letter).

The original NDA 21-121 for OROS methylphenidate was submitted 7-15-99. Safety updates were submitted at 4 months (12-20-99) and 7 months (2-15-00).

We decided not to take OROS methylphenidate to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

The chemistry review was conducted by Donald Klein, Ph.D. As of this time, I am not aware of any chemistry issues that would preclude the approvability of Concerta. The name "Concerta" has been approved by OPDRA.

3.0 PHARMACOLOGY

The original pharmacology/toxicology review was conducted by Barry Rosloff, Ph.D. As of this time, I am not aware of any pharmacology/toxicology issues that would preclude the approvability of Concerta.

4.0 BIOPHARMACEUTICS

The biopharmaceutics review was conducted by Iftekhar Mahmood, Ph.D. and Maria Sunzel, Ph.D. As of this time, I am not aware of any biopharmaceutics issues that would preclude the approvability of Concerta.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

The sponsor has provided data from 3 placebo-controlled clinical studies in children with ADHD in support of the efficacy claim for OROS methylphenidate. These included 2 essentially identical 3-way crossover trials (C-98-003 and C-97-025) involving OROS methylphenidate, IR methylphenidate, and placebo, and a 4-week, parallel group trial involving OROS methylphenidate, IR methylphenidate, and placebo. These 3 trials were the focus of our efficacy review.

The primary outcome for all 3 studies was the Inattention/Overactivity (I/O) subscale from the IOWA Conners Rating Scale, Teachers version. This includes 5 items, each rated on a scale of 0-3, giving a range for this subscale of 0 to 15. The SKAMP was used in the 2 crossover studies for assessing duration of effect.

The efficacy data were reviewed by Andrew Mosholder, M.D. of the clinical group and Yuan-Li Shen, Dr. PH of the biometrics group.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study C-98-003

This was a randomized, double-blind, 3-way crossover (6 sequence), single center study involving 1 week periods of treatment with each of OROS methylphenidate, IR methylphenidate, and placebo in n=63 children aged 6-12 with ADHD (DSM-IV) who were already considered responders to methylphenidate. The methylphenidate dose was determined based on previous methylphenidate dose, and was given either qd at 7:30 am (for OROS) or tid at 7:30 am, 11:30 am and 3:30 pm (for IR). The dosing ratio was 18 mg OROS qd to 5 mg IR tid. The doses could OROS 18 mg, 36 mg, or 54 mg, or the equivalent in IR. The IOWA Conners was obtained weekly and the SKAMP was obtained periodically throughout the day during a laboratory classroom session on the final day of each 7-day treatment period. The SKAMP assessments were at the following times after the initial 7:30 am dosing: 1, 2, 3, 5, 7, 9, 10, 11, and 12 hours. As noted, the primary outcome was designated as the I/O subscale of the IOWA Conners Teachers version. The primary efficacy analysis was designated as a mixed effects ANOVA, with the primary comparison being OROS vs placebo.

The mean age was 9, and the sample was 81% male and roughly 83% Caucasian. 61 patients were available for the analysis.

The mean IOWA Conners I/O scores after 1 week of treatment were as follows:

OROS	6.5
IR	6.9
Pbo	11.6

The methylphenidate vs placebo comparisons were highly significant ($p<0.001$) for both formulations. The sponsor checked for period effect and treatment-by-period interaction and reported no treatment-by-period interaction. However, there was a period effect, with the worst results during the first period.

Based on the sponsor's approach of averaging SKAMP data across all 3 periods, the pairwise comparisons of methylphenidate vs placebo for the SKAMP were significant at all time points beginning at 2 hours after dosing, i.e., at 2, 3, 5, 7, 9, 10, 11, and 12 hours after dosing, for both OROS and IR.

Dr. Chen confirmed the sponsor's contention of lack of treatment-by-period interaction using an alternative method. For the SKAMP data, the period effect was quite prominent for period 1, with essentially no indication of a treatment effect during that period.

Drs. Mosholder and Shen concluded that this study supported the primary claim for overall efficacy of OROS methylphenidate, and I agree.

5.1.2.2 Study C-97-025

This identical in design to study 003, except that the n was 70.

The mean age was 9, and the sample was 89% male and roughly 94% Caucasian. 68 patients were available for the analysis.

The mean IOWA Conners I/O scores after 1 week of treatment were as follows:

OROS	4.7
IR	5.0
Pbo	10.3

The methylphenidate vs placebo comparisons were highly significant ($p<0.001$) for both formulations. The sponsor checked for period effect and treatment-by-period interaction and reported none.

Based on the sponsor's approach of averaging SKAMP data across all 3 periods, the pairwise comparisons of methylphenidate vs placebo for the SKAMP were significant at all time points

beginning at 2 hours after dosing, i.e., at 2, 3, 5, 7, 9, 10, 11, and 12 hours after dosing, for both OROS and IR.

Dr. Chen confirmed the sponsor's contention of lack of treatment-by-period interaction using an alternative method. For the SKAMP data, as for study 003, the treatment effect was not consistent across all 3 periods, however, here the effect was most pronounced in period 1.

Drs. Mosholder and Shen concluded that this study supported the primary claim for overall efficacy of OROS methylphenidate, and I agree.

5.1.2.3 Study C-98-005

This was a randomized, double-blind, parallel group, 4-week, multicenter (14 US sites) study comparing OROS methylphenidate, IR methylphenidate, and placebo in n=312 children aged 6-12 with ADHD (DSM-IV) who were already considered responders to methylphenidate. The methylphenidate dose was determined based on previous methylphenidate dose, and was given either qd (for OROS) or tid (for IR). The dosing ratio was 18 mg OROS qd to 5 mg IR tid. The doses could OROS 18 mg, 36 mg, or 54 mg, or the equivalent in IR. The IOWA Conners was obtained weekly. As noted, the primary outcome was designated as the I/O subscale of the IOWA Conners Teachers version. The primary efficacy analysis was designated as a mixed effects ANOVA, with the primary comparison being OROS vs placebo.

The mean age was 9, and the sample was approximately 83% male and roughly 84% Caucasian. 276 patients were available for the analysis (due to dropping all 30 patients from one questionable site, 5 patients who never received meds, and 1for inadequate followup). Approximately 83% of both methylphenidate groups completed to 4 weeks compared to only 51% of placebo patients.

The mean IOWA Conners I/O scores after 4 weeks of treatment were as follows:

OROS	6.0
IR	6.4
Pbo	9.8

The methylphenidate vs placebo comparisons were highly significant ($p<0.001$, LOCF) for both formulations. The OC pairwise comparisons of methylphenidate vs placebo for each week were also significant for both formulations for all 4 weeks.

Drs. Mosholder and Shen concluded that this study supported the primary claim for overall efficacy of OROS methylphenidate, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Reboxetine

Secondary Outcomes

While we are clearly in agreement with the sponsor regarding their demonstration of the overall efficacy of OROS methylphenidate in the treatment of ADHD, they had hoped for additional claims. In particular, they wanted to include in labeling claims of (1) the specific effectiveness of OROS over the course of a full day, based on SKAMP data, and (2) equivalent effectiveness compared to IR methylphenidate given tid, based on the Iowa conners I/O subscale data. In my view, the principle reason for rejecting these claims is that they were not specified as primary objectives of these studies. Thus, if the studies had not succeeded on these additional outcomes, the studies could still have been considered positive and there would have been no requirement to include any negative information in labeling. In addition, there was no prior agreement about the proposed 1.2 units of the Iowa Conners I/O subscale as the upper limit for the confidence interval of difference between treatments as being clinically meaningful. An additional problem with the claim of effectiveness over a 12 hour time period is the inconsistency of the findings across different periods for the two crossover studies. Nevertheless, I think they have demonstrated the effectiveness of OROS methylphenidate on an instrument that essentially integrates in the clinician's view the benefits over the course of a day, and I think we can reflect that impression adequately in labeling in order to imply that OROS methylphenidate is effective overall in the treatment of this condition.

Evidence Bearing on the Question of Dose/Response for Efficacy

All three studies were flexible dosing, and thus, there is no information in this development pertinent to dose/response for efficacy.

Clinical Predictors of Response

While various exploratory analyses revealed some suggestions of interactions based on demographic factors or baseline scores, these findings were not consistent enough to justify any definitive statements about such effects.

Size of Treatment Effect

While it is difficult to assign clinical significance to the observed differences between OROS and placebo on the Iowa Conners I/O subscale, these differences are similar to those seen in other studies considered by most experts proof of efficacy of the IR product and were indistinguishable from the IR/placebo differences observed in these studies. Thus, I consider these clinically meaningful results.

Duration of Treatment

There were no data presented in this program pertinent to the question of longer term efficacy of OROS methylphenidate in ADHD.

5.1.3 Conclusions Regarding Efficacy Data

In summary, I consider studies 003, 025, and 005 positive support for the claim of short-term effectiveness of OROS methylphenidate in the treatment of ADHD.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for OROS methylphenidate, including the original submission and the 2 safety updates, were reviewed by Dr.Andrew Mosholder (review dated 3-23-00). This original review was based on an integrated database (with a cutoff date of 10-31-99).

There were 9 studies in normal adults (PK), and 8 clinical studies in children with ADHD (ages ranging from 6 to 13). 755 human subjects were exposed to OROS methylphenidate in the sponsor's development program, including 286 adults in phase 1 studies and 469 children with ADHD in phase 2-3 studies. The total person-years of exposure for patients in the phase 2-3 depression program was 328 for OROS methylphenidate, 10 for immediate release methylphenidate, and 8 for placebo. Patients in phase 2-3 studies were roughly 80% male and predominantly white. The median age of patients was 9. An open label extension provided for longer term exposure ($\geq$6 months) for at least half of these patients.

5.2.2 Adverse Event Profile for Concerta

5.2.2.1 Common Adverse Event Profile

The adverse event profile for Concerta was similar to that known for other methylphenidate, including notably insomnia, anorexia, and abdominal pain. The most common and drug-related adverse events leading to discontinuation included tics, anorexia, insomnia, hostility and somnolence. The two laboratory classroom clinical trials revealed the expected drug-related increases in diastolic blood pressure (mean increase of 2-6 mmHg) and pulse rate (mean increase of 2-6 bpm).

5.2.2.2 Adverse Event Issues Requiring Comment

5.2.2.2.1 GI Risks Related to Elimination of the Residual Product (Shell/Core)

The primary GI concern with this formulation is the possibility of obstruction given that the capsule shell/core needs to be eliminated after release of the drug. Obstruction has been reported, but rather uncommonly, with other OROS products. A GI irritation study in dogs revealed no evidence of GI lesions. Our consultant from HFD-180 (Dr. Joseph) recommended stronger labeling than the sponsor's proposed labeling regarding potential GI obstruction, given that the OROS methylphenidate product is one of the largest such products that will be marketed. We have, in fact,

proposed stronger labeling regarding this concern, including a contraindication for patients who might be atg particular risk of obstruction.

5.2.2.2.2 Drug Abuse Potential

Methylphenidate is a stimulant with a recognized potential for abuse, and other marketed formulations of this drug have a CSA schedule II classification. Although the sponsor has suggested that this formulation, which is given only once a day compared to 2 or 3 daily administrations for the immediate release formulation, may have a lower potential for abuse, they have not attempted to demonstrate this advantage and have not asked for a higher CSA schedule. Mike Klein, Ph.D. reviewed the drug abuse data pertinent to this application (see review dated 1-6-00) and concluded that the proposed scheduling is appropriate.

5.2.2.3 Conclusions Regarding Safety Data

Overall, there were no adverse event findings observed in the clinical trials with OROS methylphenidate that would preclude an approvable action. The adverse event profile observed is similar to that seen with other methylphenidate formulations and it can be adequately characterized in labeling. Theoretical concerns about the GI risks can also be adequately conveyed to prescribers in labeling.

5.3 Clinical Sections of Labeling

We have substantially rewritten the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

There was not published literature to review that was specifically pertinent to the OROS methylphenidate product. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, OROS methylphenidate is not approved anywhere at this time. We will ask for an update on the regulatory [redacted] approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take OROS methylphenidate to the PDAC.

9.0 DSI INSPECTIONS

Several sites were inspected, spanning all three studies that are the basis for our approvable recommendation, as follows:

Pelham for 025 and 005
Swanson/Wigal for 003 and 005
Biederman for 005.

While there were minor deviations at one site, overall, all data from all sites were deemed acceptable in support of this NDA.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft from February, 2000.

10.2 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, regulatory status update, and several other requests for additional data, responses to questions, etc.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Alza has submitted sufficient data to support the conclusion that OROS methylphenidate is effective and acceptably safe in the treatment of ADHD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDA 21-121
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/AHomonnay

DOC: ———————

APPROVABLE LETTER
ATTACHMENT 1
FDA LABELING PROPOSAL

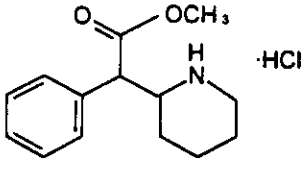
Note: Brackets [] embedded within the text that follows include comments and explanations concerning the proposed draft labeling. For some sections, few changes were proposed, while others required extensive modification. This revision is based on the version of labeling submitted February, 2000. If you feel that further revisions to this draft are necessary, please use this exact document as the starting document. Please use the 'strikeout' font to indicate the material you wish to delete and shading to indicate the material you wish to add.

CONCERTA CII
CONCERTA (methylphenidate HCl) Extended-release Tablets

DESCRIPTION

[

CONCERTA™ is a central nervous system (CNS) stimulant. CONCERTA™ is available in two tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18 or 36 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl -phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \bullet HCl$. Its structural formula is:



Methylphenidate HCl USP is a white, odorless 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. Its molecular weight is 269.77.

CONCERTA™ also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hydroxypropyl

methylcellulose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

System Components and Performance

CONCERTA™ uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble mass.

CLINICAL PHARMACOLOGY

Pharmacodynamics

[We have modified your proposed language.]

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monamines into the extranueronal space. Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

Pharmacokinetics

[We have added statements to indicate that the pharmacokinetic data described are chiefly from adult subjects.]

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA™ to adults, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 to 2 hours, then increase gradually over the next several hours. Peak plasma concentrations are achieved at about 6 to 8 hours after which a gradual decrease in plasma levels of methylphenidate begins. CONCERTA™ qd minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate tid (see Figure 1). The relative bioavailability of CONCERTA™ qd and methylphenidate tid in adults are comparable.

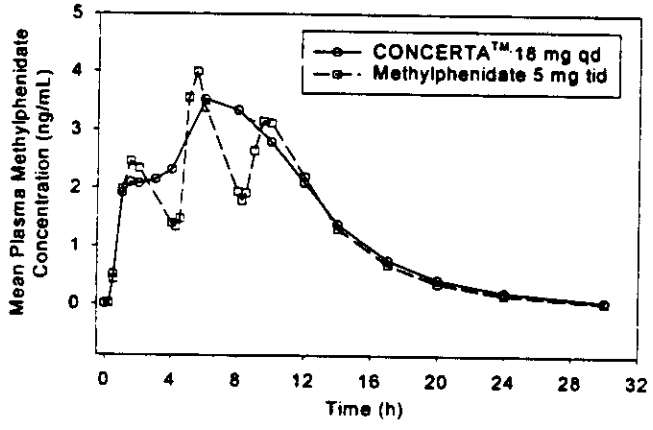


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA™ 18 mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours.

The mean pharmacokinetic parameters in 36 adults following the administration of CONCERTA™ 18 mg qd and methylphenidate 5 mg tid are summarized in Table 1.

[Here, we have added the units for t ½ and the standard deviations.]

Table 1
Mean+/-SD Pharmacokinetic Parameters

Parameters	CONCERTA™ (18 mg qd)	Methylphenidate (5 mg tid)
C_{max} (ng/mL)	3.7 +/- 1.0	4.2 +/- 1.0
T_{max} (h)	6.8 +/- 1.8	6.5 +/- 1.8
AUC_{inf} (ng·h/mL)	41.8 +/- 13.9	38.0 +/- 11.0
t ½ (h)	3.5 +/- 0.4	3.0 +/- 0.5

No differences in the pharmacokinetics of CONCERTA™ were noted following single and repeated qd dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated qd dosing are similar to those following the first dose of CONCERTA™ 18 mg.

Dose Proportionality

[We have slightly modified the following subsection.]

Following administration of CONCERTA™ in single doses of 18, 36, and 54 mg/day to adults, Cmax and $AUC_{(0\text{-inf})}$ of d-methylphenidate were proportionate to dose, whereas l-methylphenidate Cmax and $AUC_{(0\text{-inf})}$ increased disproportionately with respect to dose. Following administration of CONCERTA™, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

Distribution

Plasma methylphenidate concentrations in adults decline biexponentially following oral administration. The half-life of methylphenidate in adults following oral administration of CONCERTA™ was approximately 3.5 h.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to alpha-phenyl-piperidine acetic acid (PPA) which has little or no pharmacologic activity. In adults the metabolism of CONCERTA™ qd as evaluated by metabolism to PPA is similar to that of methylphenidate tid. The metabolism of single and repeated qd doses of CONCERTA™ is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

Food Effects

[We have made minor editorial changes to the following subsection.]

In patients, there were no differences in the pharmacokinetics and pharmacodynamic performance of CONCERTA™ when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations

Gender

In healthy adults, the mean dose-adjusted $AUC_{(0\text{-}inf)}$ values for CONCERTA™ were 36.7 ng·h/mL in men and 37.1 ng·h/mL in women, with no differences noted between the two groups.

Race

[Below, we have added a statement that the sample size to evaluate ethnic pharmacokinetic differences was small.]

In adults receiving CONCERTA™, dose adjusted $AUC_{(0\text{-}inf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

The pharmacokinetics of Concerta has not been studied in children less than 6.

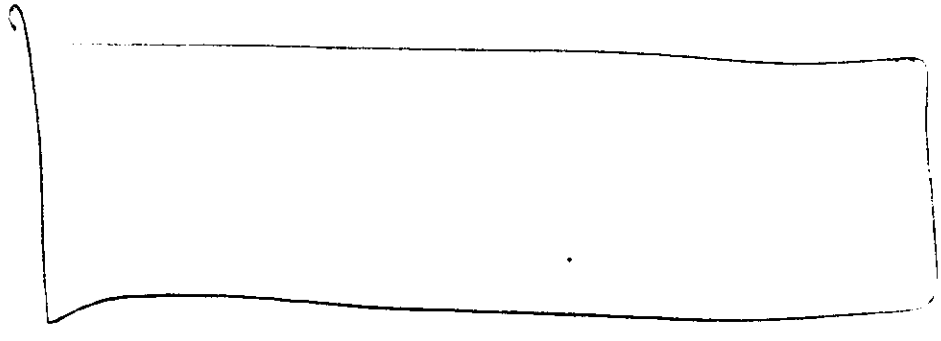
Renal Insufficiency

There is no experience with the use of CONCERTA™ in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA™.

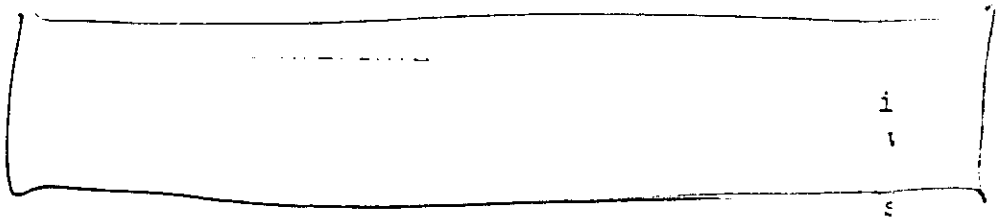
Hepatic Insufficiency

There is no experience with the use of CONCERTA™ in patients with hepatic insufficiency.

Clinical Studies



-We have also removed the claim of long term efficacy-



CONCERTA™ was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in three double-blind, active- and placebo-controlled studies in 416 children 6 to 12 years old. The controlled studies compared CONCERTA™ given qd (18, 36, or 54 mg), methylphenidate given tid over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was for Concerta versus placebo.

The Diagnostic and Statistical Manual, 4th edition, of the American Psychiatric Association (DSM-IV) provides criteria for three subtypes of ADHD (Combined Type, Predominantly Inattentive Type, or Predominantly Hyperactive-Impulsive Type). These criteria were used for diagnosis in all three studies.

Symptoms of ADHD were evaluated by community school teachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA™ qd. The scores for Concerta and placebo for the three studies are presented in Figure 2.

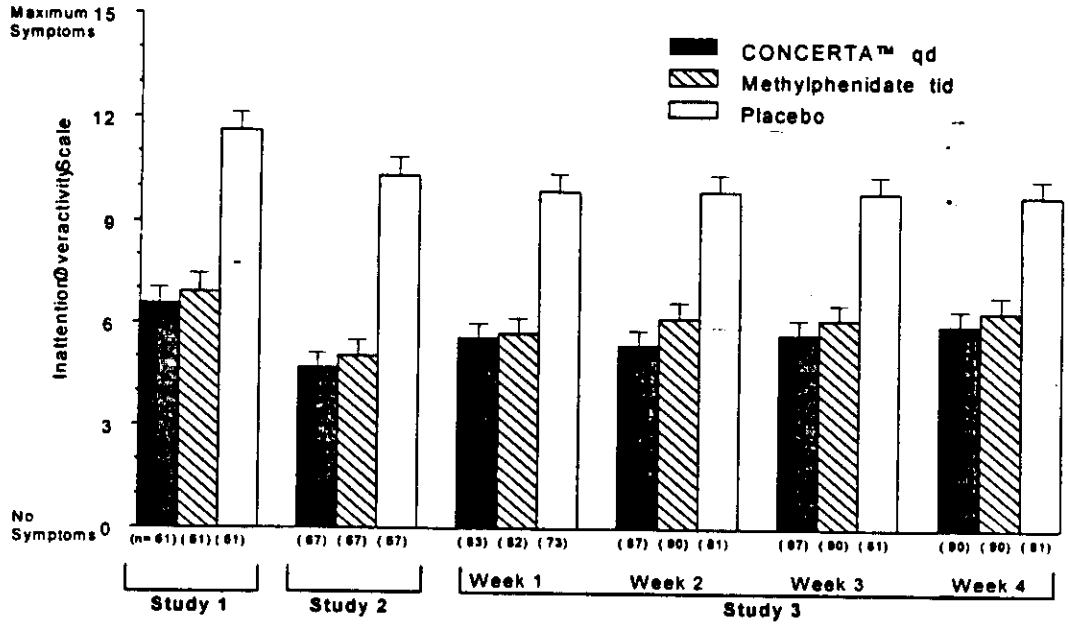


Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA™ qd (18, 36, or 54 mg), methylphenidate tid over 12 hours (15, 30, or 45 mg total daily dose), and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group treatments with a Last Observation Carried Forward analysis for weeks 2 to 4. Error bars represent mean plus standard error of mean.

INDICATION AND USAGE

[We have extensively edited this section to make it consistent with the current style and content in psychotropic labeling. We have added certain language from current Ritalin labeling pertaining to the need for careful diagnosis and a comprehensive treatment program for this population.]

Attention Deficit Hyperactivity Disorder (ADHD)

Concerta is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of Concerta in the treatment of ADHD was established in three controlled trials of children aged 6 to 12 who met DSM-IV criteria for ADHD (see Clinical Pharmacology).

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be

present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Types requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

CONCERTA™ is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use

The effectiveness of Concerta for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Concerta for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see Dosage and Administration).

CONTRAINDICATIONS

[s. We have added a contraindication for monoamine oxidase inhibitors, We have also added a contraindication regarding gastrointestinal disorders. We have added subheadings to this section.]

Agitation

CONCERTA™ is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate

CONCERTA™ is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma

CONCERTA™ is contraindicated in patients with glaucoma.

Tics

CONCERTA™ is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome. CNS stimulants, including methylphenidate, have been associated with the onset or exacerbation of motor and verbal tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children should precede use of stimulant medication. Family history should be assessed. In a long term open label treatment study (n=407 children), the cumulative incidence of new onset of tics was 8% after 8 months of treatment with CONCERTA™.

Predisposition to Gastrointestinal Obstruction

Because it is a nondeformable dosage formulation, CONCERTA™ is contraindicated in patients who have a predisposition to gastrointestinal obstruction. Patients with any of the following conditions should not use CONCERTA™:

Strictures of the gastrointestinal tract
Small bowel inflammatory disease
"Short gut" syndrome due to adhesions or decreased transit time
Past history of peritonitis
Cystic fibrosis
Chronic intestinal pseudoobstruction

Meckel's diverticulum

Monoamine Oxidase Inhibitors

CONCERTA™ is contraindicated during treatment with monoamine oxidase inhibitors, and also within a minimum of 14 days following discontinuation of a monoamine oxidase inhibitor (hypertensive crises may result).

WARNINGS

[We have added subheadings to the Warnings section. For tic disorders, we have added the results from your 3/28/00 fax describing the cumulative incidence of new tics in study C98012. We have restored the language from the Ritalin labeling regarding visual disturbance, which we believe reads more easily.

. We have restored the paragraphs about long term use and treatment of fatigue, and added a statement about use in children under age 6 years.]

Depression

CONCERTA™ should not be used to treat severe depression.

Fatigue

CONCERTA™ should not be used for the prevention or treatment of normal fatigue states.

Long-Term Supression of Growth

Sufficient data on the safety of long-term use of methylphenidate in children are not yet available. Although a causal relationship has not been established, suppression of growth (i.e., weight gain, and/or height) has been reported with the long-term use of stimulants in children. Therefore, patients requiring long-term therapy should be carefully monitored. Patients who are not growing or gaining weight as expected should have their treatment interrupted.

Psychosis

Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of

behavior disturbance and thought disorder.

Seizures

There is some clinical evidence that methylphenidate may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in absence of history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Hypertension and other Cardiovascular Conditions

Use cautiously in patients with hypertension. Blood pressure should be monitored at appropriate intervals in patients taking CONCERTA™, especially patients with hypertension. In the laboratory classroom clinical trials, both CONCERTA™ and methylphenidate tid produced average increases of systolic and diastolic blood pressure of roughly 2-6 mm Hg during the day, relative to placebo. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, e.g., those with pre-existing hypertension, heart failure, or recent myocardial infarction.

Likewise, in the same laboratory classroom studies, both methylphenidate treatments increased resting pulse by 2-6 bpm during the day. Accordingly, CONCERTA™ should be used with caution in patients whose underlying medical conditions might be compromised by increases in heart rate, e.g., patients with hyperthyroidism, heart failure, or recent myocardial infarction.

Visual disturbance

Symptoms of visual disturbances have been encountered in rare cases. Difficulties with accommodation and blurring of vision have been reported.

Use in Children Under Six Years of Age

CONCERTA™ should not be used in children under six years, since safety and efficacy in this age group have not been established. In addition, the large size of the nondeformable tablets may pose a risk of gastrointestinal adverse reactions in younger children (see Precautions).

DRUG DEPENDENCE

CONCERTA™ should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

[We have added a statement about the size of the tablet as it applies to the potential for gastrointestinal obstruction. We have also added subheadings to the Precautions section. We have restored the statement about hematologic monitoring that appears in the labeling for Ritalin.]

Potential for gastrointestinal obstruction

As with any other nondeformable material, caution should be used when administering CONCERTA™ to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). See CONTRAINDICATIONS. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations. **Due to the large size of the tablet, special care should be taken when using this product in younger children (under 12 years of age).**

Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients

Patients should be informed that CONCERTA™ should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Patient information is printed at the end of this insert. To assure safe and effective use of Concerta, the information and instructions provided in the patient information section should be discussed with patients.

Drug Interactions

[We have added a statement about monitoring plasma drug concentrations for concomitant drugs likely to have a metabolic interaction with methylphenidate. We have revised your proposed

statement regarding concomitant clonidine.]

Because of possible effects on blood pressure, CONCERTA™ should be used cautiously with pressor agents.

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha 2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

[For calculations of animal-to-human safety factors, we have used a maximum human dose of 2 mg/kg, and human mg/kg-to-mg/m^2 multipliers of 25 and 31 for the carcinogenicity and

[redacted]

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA™ on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA™ on a mg/kg and mg/m^2 basis, respectively.

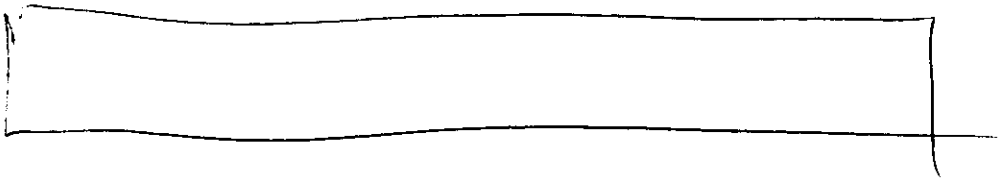
In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay.

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA™ on a mg/kg and mg/m^2 basis, respectively.

Pregnancy: Teratogenic Effects

[We have added recent changes to the Ritalin labeling noting findings from a rabbit reproductive toxicity study. We are accordingly assigning the drug to reproduction category C.



Pregnancy Category C: Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA™ on a mg/kg and mg/m^2 basis, respectively. Plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was approximately [see above] times that seen in trials in patients with the maximum recommended dose of CONCERTA™ based on the AUC.

There are no adequate and well-controlled studies in pregnant women. CONCERTA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

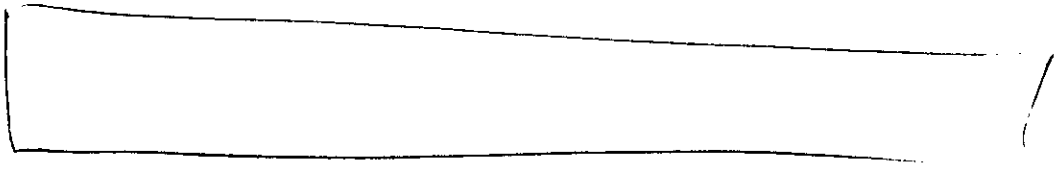
Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA™ is administered to a nursing woman.

Pediatric Use

The safety and efficacy of CONCERTA™ in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (See Warnings).

ADVERSE REACTIONS



adverse events profile. We have included all events rather than limiting the table to events considered by the investigators to be drug related. We have added information on discontinuation. We have changed the number of patients to 469, consistent with your most recent safety update. Under your proposed heading, "Adverse Events with Other Methylphenidate HCl Products," we have restored this statement to the exact language from the current Ritalin labeling.]

The premarketing development program for Concerta included exposures in a total of 755 participants in clinical trials (469 patients, 286 healthy adult subjects). These participants received Concerta 18, 36, and/or 54 mg/day. The 469 patients (ages 6 to 13) were evaluated in three controlled clinical studies (Studies 1, 2, and 3), two uncontrolled clinical studies (including a long-term safety study), and one clinical pharmacology study in children with ADHD. All patients studied had previously received methylphenidate for ADHD. Accordingly, there is no data on adverse reactions to CONCERTA□ among children naive to methylphenidate treatment. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory

analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with Concerta

Adverse Events Associated with Discontinuation of Treatment

Among all clinical trials experience with Concerta, 6.4% (30/469) Concerta-treated patients discontinued for adverse events compared to 1.4% (4/276) of placebo-treated patients. Those events associated with discontinuation from Concerta in more than 1 patient and for which the risk of discontinuation exceeded the placebo risk included the following: twitching; anorexia; insomnia; hostility; and somnolence. Twitching, which in every case was identified as tics, was the most common reason for discontinuing Concerta treatment.

Adverse Events Occurring at an Incidence of 1% or more Among Sonata 20 mg-Treated Patients

Table 1 enumerates, for a 4-week placebo-controlled, parallel-group trial in children with ADHD at Concerta doses of 18, 36, or 54 mg/day, the incidence of treatment emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with Concerta where the incidence in patients treated with Concerta was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however,

do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1
Incidence (%) of Treatment-Emergent Events[1] in a 4-Week Placebo-Controlled Clinical Trials of Concerta

Body system Preferred Term	Placebo (n=238)	Concerta (n=234)
Headache	10	14
Abdominal pain	1	7
Vomiting	3	4
Anorexia	0	4
Dizziness	0	2
Insomnia	1	4
Upper Respiratory Tract Infection	5	8
Cough Increased	2	4
Pharyngitis	3	4
Sinusitis	0	3

1:Events for which the incidence for Concerta-treated patients was at least1% and greater than the incidence among placebo-treated patients. Incidence greater than 1% has been rounded to the nearest whole number.

Adverse Events with Other Methylphenidate HCl Products

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting methylphenidate in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: instances of abnormal liver function, ranging from transaminase elevation to hepatic coma; isolated cases of cerebral arteritis and/or occlusion; leukopenia and/or anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an

NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

[We have made minor changes to the format of this section.]

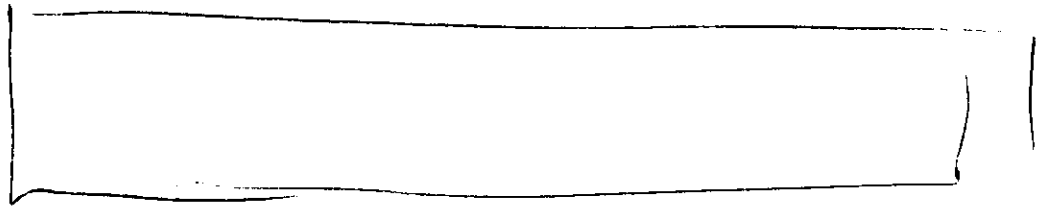
Controlled Substance Class

CONCERTA™, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance

See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE



Signs and Symptoms

Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage; before performing gastric lavage, control agitation and seizures and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CONCERTA™ overdosage has not been established.

The prolonged release of methylphenidate from CONCERTA™ should be considered when treating patients with overdose.

Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

DOSAGE AND ADMINISTRATION

[We have slightly edited Table 3. We have restored some language from the current Ritalin Dosage and Administration labeling.]

CONCERTA™ must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed. See PRECAUTIONS: Information for Patients.

CONCERTA™ may be administered with or without food and should be administered once daily in the morning.

Dosage should be individualized according to the needs and responses of the patient.

Patients New to Methylphenidate

The recommended starting dose of CONCERTA™ for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Patients Currently Using Methylphenidate

The recommended dose of CONCERTA™ for patients who are currently taking methylphenidate bid, tid, or sustained-release (SR) at doses of 10 to 60 mg/day is provided in Table 3. Dosing recommendations are based on current dose regimen and clinical judgement.

Dosage may be adjusted in 18 mg increments to a maximum of 54 mg/day taken once daily in the morning. In general, dosage adjustment may proceed at approximately weekly intervals.

Table 3
Recommended Dose Conversion from
Methylphenidate Regimens to CONCERTA™

Previous Methylphenidate Daily Dose	Recommended CONCERTA™ Dose
5 mg Methylphenidate bid or 5 mg Methylphenidate tid or 20 mg Methylphenidate-SR	18 mg q am
10 mg Methylphenidate bid or 10 mg Methylphenidate tid or 40 mg Methylphenidate-SR	36 mg q am
15 mg Methylphenidate bid or 15 mg Methylphenidate tid or 60 mg Methylphenidate-SR	54 mg q am

Other methylphenidate regimens: Clinical judgement should be used when selecting the starting dose.

Daily dosage above 54 mg is not recommended.

Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Concerta. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Concerta for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

HOW SUPPLIED

[No changes in this section.]

CONCERTA™ (methylphenidate HCl) Extended-release Tablets are available in 18 mg and 36 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". The 36 mg tablets are white and imprinted with "alza 36". Both dosage strengths are supplied in bottles containing 30 or 100 tablets.

18 mg	30 count bottle	NDC 17314-5850-1
	100 count bottle	NDC 17314-5850-2
36 mg	30 count bottle	NDC 17314-5851-1
	100 count bottle	NDC 17314-5851-2

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.

REFERENCE

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

INFORMATION FOR PATIENTS TAKING CONCERTA OR THEIR PARENTS OR CAREGIVERS

[-This section should be included both as part of the package insert, and also as a separate document for distribution. We have added a statement about symptoms of ADHD needing to be present for 6 months to be certain of the diagnosis. We have , as . With respect to side effects, we have amended the description to reflect the labeling for Ritalin. We have added a statement that the drug may be habit forming, and that it should not be taken with monoamine oxidase inhibitors, and have made a few other editorial changes.]

CONCERTA (methylphenidate HCl) Extended-release Tablets CII

This information is for patients or their parents or caregivers taking CONCERTA Extended-release tablets CII for the Treatment of Attention Deficit/ Hyperactivity Disorder.

Please read this before you start taking CONCERTA. Remember, this information does not take the place of your doctor's instructions. If you have any questions about this information or about CONCERTA, talk to your doctor or pharmacist.

What is CONCERTA?

CONCERTA is a once-a-day treatment for Attention Deficit/Hyperactivity Disorder, or ADHD. CONCERTA contains the drug methylphenidate, a central nervous system stimulant that has been used to treat ADHD for more than 30 years. CONCERTA is taken by mouth, once each day in the morning.

What is Attention Deficit/Hyperactivity Disorder?

ADHD has three main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all three types of symptoms.

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

How does CONCERTA work?

Part of the CONCERTA tablet dissolves right after you swallow it in the morning, giving you an initial dose of methylphenidate. The remaining drug is slowly released during the day to continue to help lessen the symptoms of ADHD. Methylphenidate, the active ingredient in CONCERTA, helps increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Who should NOT take CONCERTA?

You should NOT take CONCERTA if:

- You have significant anxiety, tension, or agitation since CONCERTA may make these conditions worse.
- You are allergic to methylphenidate or any of the other ingredients in CONCERTA.
- You have glaucoma, an eye disease.
- You have tics or Tourette's Syndrome, or a family history of Tourette's Syndrome
- You have a disorder of the gastrointestinal tract (stomach and intestines) that might lead to blockage by CONCERTA tablets.

Talk to your doctor if you believe any of these conditions apply to you.

How should I take CONCERTA?

Do not chew, crush, or divide the tablets. Swallow CONCERTA tablets whole with the help of water or other liquids, such as milk or juice.

Take CONCERTA once each day in the morning.

You may take CONCERTA before or after you eat.

Take the dose prescribed by your doctor. Your doctor may adjust the amount of drug you take until it is right for you. From time to time, your doctor may interrupt your treatment to check your symptoms while you are not taking the drug.

What are the possible side effects of CONCERTA?

In the clinical studies with patients using Concerta, the most common side effects were headache, stomach pain, sleeplessness, and decreased appetite. Other side effects seen with methylphenidate, the active ingredient in Concerta, include nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure and psychosis (abnormal thinking or hallucinations).

This is not a complete list of possible side effects. Ask your doctor about other side effects. If you develop any side effect, talk to your doctor.

What must I discuss with my doctor before taking CONCERTA?

Talk to your doctor ***before*** taking CONCERTA if you:

- Are being treated for depression or have symptoms of depression such as feelings of sadness, worthlessness, and hopelessness.
- Have motion tics (hard-to-control, repeated twitching of any parts of your body) or verbal tics (hard-to-control repeating of sounds or words).
- Have someone in your family with motion tics, verbal tics, or Tourette's syndrome.
- Have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis.
- Have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms).
- Have high blood pressure.
- Have a narrowing or blockage of your gastrointestinal tract (your esophagus, stomach, or small or large intestine).

Tell your doctor ***immediately*** if you develop any of the above conditions or symptoms while taking CONCERTA.

Can I take CONCERTA with other medicines?

Tell your doctor about ***all*** medicines that you are taking. Your doctor should decide whether you can take CONCERTA with other medicines. These include:-

Other medicines that a doctor has prescribed.
Medicines that you buy yourself at the pharmacy.
Any herbal remedies that you may be taking.

You should not take CONCERTA with monoamine oxidase (MAO) inhibitors.

While on CONCERTA, do not start taking a new medicine or herbal remedy before checking with your doctor.

CONCERTA may change the way your body reacts to certain medicines. These include medicines used to treat depression, prevent seizures, or prevent blood clots (commonly called "blood thinners"). Your doctor may need to change your dose of these medicines if you are taking them with CONCERTA.

Other Important Safety Information

CONCERTA may be habit forming (addictive).

Tell your doctor if you have ever abused or been dependent on alcohol or drugs, or if you are now abusing or dependent on alcohol or drugs.

Before taking CONCERTA, tell your doctor if you are pregnant or plan on becoming pregnant. If you take methylphenidate, it may be in your breast milk. Tell your doctor if you are nursing a baby.

Tell your doctor if you have blurred vision when taking CONCERTA.

Slower growth (weight gain and/or height) has been reported with long-term use of methylphenidate in children. Your doctor will be carefully watching your height and weight. If you are not growing or gaining weight as your doctor expects, your doctor may interrupt your CONCERTA treatment.

Call your doctor ***immediately*** if you take more than the amount of CONCERTA prescribed by your doctor.

What else should I know about CONCERTA?

CONCERTA has not been studied in children under 6 years of age.

The CONCERTA tablet does not dissolve completely after all the drug has been released, and you may sometimes notice it in your stool. This is normal.

CONCERTA may be a part of your overall treatment for ADHD. Your doctor may also recommend that you have counseling or other therapy.

As with all medicines, never share CONCERTA with anyone else and take only the number of CONCERTA tablets prescribed by your doctor.

CONCERTA should be stored in a safe place at room temperature (between 59□□86□ F). Do not store this medicine in hot, damp, or humid places.

Keep out of the reach of children.

Doc ORSLBAE2.DOC