CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-284

ADMINISTRATIVE DOCUMENTS

Patent Submission

Time Sensitive Patent Information

pursuant to 21 C.F.R. 314.53

for

NDA # 21-008

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Ritalin LA
- Active Ingredient(s): Methylphenidate HCl
- Strength(s): 20, 30, and 40 mg
- Dosage Form: Modified Release Capsules
- Approval Date: Approval currently sought

A. This section should be completed for each individual patent

U.S. Patent Number: 5,837,284

Expiration Date: May 15, 2016

Type of Patent--Indicate all that apply:

1.	Drug substance (Active Ingredient)	x Y	N
2.	Drug Product (Composition/Formulation	x Y	N
3.	Method of Use	Y	x N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent

---

Name of Patent Owner: Celgene Corporation

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

(for purposes of this document only)
General Counsel
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,837,284 covers the composition, formulation and/or method of use of Ritalin LA. This product is:

- ____ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- X the subject of this application for which approval is being sought.)

Signed: John S. Kabnick, Patent + Trademark Reg. No. 38,747
Date: 12/24/00
Title (optional): Senior Patent Attorney
Telephone Number (optional):

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the ***The Orange Book,**** a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OF

Location address: (for FedX deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

EXCLUSIVITY SUMMARY for NDA # 21-284

Trade Name Ritalin® LA Generic Name methylphenidate HCl

Applicant Name Novartis Pharmaceuticals HFD- 120
Approval Date June 7, 2002

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" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) 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 /_X_/ 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 your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      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:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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.

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 already approved active moiety.

YES /_X__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-121 Concerta

NDA # 21-259 Metadate CD

NDA # 10-187 Ritalin

2. Combination product.

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 under 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).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The 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 /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 not 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 trials, 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), or 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 some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(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 /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any 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 /_X__/

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 # Protocol 02

Investigation #2, Study # Protocol 07

Investigation #3, Study # _____

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 relied 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 the 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 approved 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 /X/
Investigation #2	YES /___/	NO /X/
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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /_X__/
Investigation #2	YES /___/	NO /_X__/
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:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) 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 that are not "new"):

Investigation #_1_, Study # __Protocol 02_____

Investigation #_2_, Study # __Protocol 07_____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have 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

_____ YES /_X_/ ! NO /___/ Explain: _____

Investigation #2

_____ YES /_X_/ ! NO /___/ 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 interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "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: _____

_____

_____

Anna Marie H. Weikel, R.Ph. Date 5/30/02
Signature of Preparer

Title: Regulatory Health Project Manager

/S/ 6/3/02
Signature of Office of Division Director Date

cc:

Archival NDA
HFD-120/Division File
HFD-120/Homonnay
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-284 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 11/29/00 Action Date: 6/7/02

HFD 120 Trade and generic names/dosage form: Ritalin LA Extended-release Capsules

Applicant: Novartis Therapeutic Class: 3

Indication(s) previously approved: na

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Tx of ADHD in children aged 6-12 yrs

Is there a full waiver for this indication (check one)?

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☑ Other: methodology for studying disease in pre-schoolers ill-defined

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: _____

Redacted 5

pages of trade secret and/or confidential commercial information

NDA No.21-284

Ritalin® LA
(methylphenidate hydrochloride) Modified-Release Capsules
New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

11/27/00
Date

Mara Stiles
Associate Director
Drug Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: September 6, 2001

TO: Anna Marie Homonnay, 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: Gerald R. Hajarian

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-284

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: Ritalin LA (methylphenidate HCl)

CHEMICAL CLASSIFICATION: Type 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

CONSULTATION REQUEST DATE: Unknown

ACTION GOAL DATE: September 29, 2001

I. BACKGROUND:

Inspection assignments were issued on March 12, 2001 for two domestic clinical investigators for Protocol 07 for the purpose of validating data in support of pending NDA 21-284.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
[redacted]			3-12-2001	June 2001	NAI
[redacted]			3-12-2001	June 2001	NAI

A. [redacted]

Fufteen (15) subjects were enrolled, twelve (12) of whom completed the study. Three subjects discontinued - one due to relocation, and two subjects were discontinued at the sponsor's request because they were in kindergarten rather than elementary school. Records of twelve (12) subjects were audited. No objectionable conditions were noted and no Form FDA 483 was issued. The data are acceptable.

B. [redacted]

Twenty-one (21) subjects were enrolled, twenty (20) of whom completed the study. One subject withdrew consent. No objectional conditions were noted and no Form FDA 483 was issued. The data are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data from both sites appear acceptable for use in support of pending NDA 21-284.

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

Gerald R. Hajarian
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47

Division of Scientific Investigations

cc:
NDA 21-284
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s
HFD-47/Hajarian
HFD-47/Thomas
HFD-45/RF
rd:grh:9/5/01

O:\GRH\NDA21284 CIS.DOC

Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter!**

Application #(s):	NDA 21-284
Document Type:	Form
Document Group:	
Document Name:	Request for DSI Audit of Clinical Study Sites
Shortcut ID Code:	
COMIS Decision:	No Decision Code
	(MEMORANDUM (Request for Clinical Inspections))
COMIS Data Entry:	
Drafted by:	ahw/January 22, 2001
Revised by:	
Initialed by:	
Finalized:	
Filename:	C:\WPFILES\NDA\RitalinLA\dsicon.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this consult either to the initial submission of the IND, NDA, or supplement; or if this consult request pertains to specific incoming document(s), then link this consult to those specific incoming document(s).

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

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

Date: January 22, 2001

To: Connie Lewin, GCPB Reviewer/HFD-47

From: Anna Marie Homonnay, Regulatory Health Project Manager, HFD-120

Subject: **Request for Clinical Inspections**
NDA 21-284
Novartis Pharmaceuticals Corporation
Ritalin LA (methylphenidate hydrochloride) modified-release capsules

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
management of attention deficit disorder	Protocol 02	see 1/8/01 submission
management of attention deficit disorder	Protocol 07	see 1/8/01 submission

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **8/29/01**. We intend to issue an action letter on this application by (action goal date) **9/29/01**.

Should you require any additional information, please contact Anna Marie Homonnay.

Concurrence: (if necessary)

Thomas Laughren, M.D., Medical Team Leader
Andrew Mosholder, M.D., Medical Reviewer

WITHHOLD 3 PAGE (S)

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

DATE RECEIVED: 1/24/01	**DUE DATE:** 9/21/01	**OPDRA CONSULT:** 01-0034

TO:

Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH:

Anna Marie Homonnay
Project Manager, Division of Neuropharmacological Drug Products
HFD-120

PRODUCT NAME:	**MANUFACTURER:** Novartis Pharmaceuticals Corporation
Ritalin LA (methylphenidate HCl modified-release capsules) 20 mg, 30 mg, and 40 mg **NDA #:** 21-284	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA conducted a review of the proposed proprietary name "Ritalin LA" to determine the potential for confusion with approved proprietary and established names as well as pending names.

OPDRA RECOMMENDATION:
OPDRA has no objection to the use of the proprietary name, "Ritalin LA".

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3246
Fax: 301-443-5161

Martin Himmel, 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. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 14, 2001

NDA NUMBER: 21-284

NAME OF DRUG: Ritalin LA (methylphenidate HCl modified-release capsules), 20 mg, 30 mg, and 40 mg

NDA HOLDER: Novartis Pharmaceuticals Corporation

I. INTRODUCTION:

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for assessment of the tradename "Ritalin LA", regarding potential name confusion with other proprietary/established drug names.

PRODUCT INFORMATION

"Ritalin LA" is the proposed proprietary name for methylphenidate hydrochloride modified-release capsule, which is a mild central nervous system stimulant and is indicated for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). This formulation provides, in the administration of one dose, a bi-modal release profile where it mimics the twice-a-day administration of *Ritalin* tablets. Each bead-filled "Ritalin LA" capsule provides an immediate release of methylphenidate, and a second release of methylphenidate is then released approximately four hours later. "Ritalin LA" is available as a 20 mg, 30 mg, and 40 mg capsule. The recommended dose of "Ritalin LA" for patients currently taking methylphenidate twice a day or sustained release (SR) is found in the table below.

Ritalin was approved in the United States prior to January 1, 1982 while *Ritalin-SR* was approved on March 30, 1982.

Previous methylphenidate dose	Recommended Ritalin LA dose
10 mg methylphenidate twice a day or 20 mg methylphenidate-SR	20 mg once a day
15 mg methylphenidate twice a day	30 mg once a day
20 mg methylphenidate twice a day or 40 mg methylphenidate-SR	40 mg once a day

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "Ritalin LA" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[5] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[6] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, a search was conducted through the FDA Adverse Event Reporting System *(AERS)* database for all post-marketing safety reports of medication errors reported for terms "rit%", "methy%", "card%", and "meta%", using the Meddra Preferred Term, DRUG MALADMINISTRATION. A search was also conducted in the FDA DQRS database by using the terms "methylphenidate" and "Ritalin".

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Ritalin LA". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The Expert Panel had concerns about the potential risk of a medication error occurring between *Ritalin-SR* and "Ritalin LA" and was skeptical in the use of the modifier "LA" for the *Ritalin* product. The Panel also had questions about the correct use of the "SR" modifier. If the modifier "SR" means twice a day while the product *Ritalin-SR* is given once a day, then, for example, a "CD" modifier may be more appropriate.

C. SAFETY EVALUATOR RISK ASSESSMENT

According to the submission, the sponsor uses "methylphenidate hydrochloride : ~~———~~ capsules" as the establish name. However, after consulting with Dan Boring (of the USAN council and LNC) and the Division of Neuropharmacological Drug Products, there are no ~~———~~ monograph titles. Therefore, "methylphenidate hydrochloride : ~~——~~ ~~——~~ capsules" should be revised to state "methylphenidate hydrochloride extended-release capsules".

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

[6] WWW location http://www.thomson-thomson.com.

In reviewing the proprietary name "Ritalin LA", the primary concerns raised were related to the similarity to the name *Ritalin-SR*. The proprietary drug name *Ritalin* has already been established in the U.S. market. *Ritalin-SR* has been on the U.S. market since March 20, 1982 while the immediate release *Ritalin* has been on the market prior to January 1, 1982. *Ritalin-SR*, which is only available in 20 mg tablets, is an extended-release preparation of methylphenidate hydrochloride. It is more slowly, but extensively absorbed than in the immediate releasing *Ritalin* tablets. The duration of action of *Ritalin-SR* tablets is approximately 8 hours. In a brief review of existing proprietary drug names on the market with the "SR" modifier, the dosing schedules of "SR" products range from once a day to three times a day.

Like *Ritalin-SR*, "Ritalin LA" is also an extended-release drug product; however, its release mechanism is different from the *Ritalin-SR* product. "Ritalin LA" has a bi-modal release profile where it mimics the twice-a-day administration of *Ritalin* tablets. Each bead-filled "Ritalin LA" capsule provides an immediate release of methylphenidate, and a second release of methylphenidate is then released approximately four hours later. Basically, "Ritalin LA", which is available in 20 mg, 30 mg, and 40 mg capsule, is given once a day (since the medication is generally given during school hours). Both "Ritalin LA" and *Ritalin-SR* have overlapping strengths (20 mg), same route of administration (oral), and both can be given once a day (extended-release). Practitioners may have difficulty in distinguishing between the *SR* and "LA" product. The AERS and DQRS searches produced three reported errors between *Ritalin* and *Ritalin-SR*, and two reported errors regarding the confusion between *Cardizem CD* and *Cardizem SR*. The searches did not produce any medication error reports regarding *Metadate CD* and *Metadate ER*. However, when switching from the SR product to the "LA" product, it is recommended that the same strength be used in the "LA" product as in the *SR* product, implying that both have identical clinical effects. Even though they have identical duration of action, the bi-modal product should have a modifier different from *SR* since it has a different releasing mechanism and a different concentration-time profile. There would be no other way in distinguishing these two products except by using different modifiers in their proprietary names. Since "Ritalin LA" is an extended-release product, "LA" may be used as the modifier of this product. Other "LA" drug products on the market including *Inderide LA, Inderal LA, Detrol LA* are a once-a-day dosing schedule except for *Decadron-LA* (once given, may be repeated in 1 to 3 week intervals).

Metadate CD (methylphenidate hydrochloride extended-release capsule) contains both immediate-release and extended-release beads in its capsule and is given once a day. However, other *CD* preparations do not follow the same type of mechanism or dosing schedule (e.g. *Ceclor CD, Cardizem CD,* and *Lamictal CD).*

OPDRA has no objections to the use of the proprietary name "Ritalin LA".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER LABEL (20 mg, 30 mg, and 40 mg; 30 and 100 tablets)

1. The "Ritalin LA" labels are quite similar to the *Ritalin-SR* labels due to the same type of design and color. On both labels, the letter and strengths appear black and red. Both drug product labels should be distinguished from each other. A different color other than black and red should be used for the name "Ritalin LA", for example.

2. The strengths on the "Ritalin LA" labels should be distinguished from each other. They can be highlighted with each a different color or by borders.

3. The statement "Dosage: See package insert" should be revised to state "Usual Dosage: 1 capsule once a day in the morning. See package insert for further information."

B. PACKAGE INSERT

1. OPDRA has no comments.

IV. RECOMMENDATIONS:

A. OPDRA has no objections to the use of the proprietary name "Ritalin LA".

B. OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

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

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

/s/

Jennifer Fan
9/21/01 03:20:28 PM
PHARMACIST

Please sign ASAP, action date next week. Thank you.

Jerry Phillips
9/24/01 01:37:41 PM
DIRECTOR

Martin Himmel
9/25/01 10:38:52 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OPDRA Request
HFD-400
Parklawn Bldg/Room 15B-03
Attention: Sammie Beam, Project Manager

FROM: Division of Neuropharmacological Drug Products
HFD-120
Woodmont II Bldg

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/22/01		21-284		11/28/00

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ritalin LA Modified – release Capsules	**Standard Review**		**PDUFA due date 9/29/01**

NAME OF FIRM: Novartis Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **Please find attached the labeling for pending NDA 21-284. This name has been previously reviewed under the ——— If you should have any questions, please call Ms. Anna Marie Homonnay at: 594-5535**

Thank You

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

DATE SENT: September 13, 1999	**DUE DATE:** N/A	**OPDRA CONSULT #:** 99-022

TO (Division):
Russ Katz, MD
Acting Director, Division of Neuropharmacological Drug Products
(HFD-120)

PRODUCT NAME: Ritalin®-	**MANUFACTURER:** Novartis

CASE REPORT NUMBER(S): Not applicable.

SUMMARY: The Division of Neuropharmacological Drug Products requested OPDRA review the acceptability of the proposed proprietary name Ritalin®-

OPDRA RECOMMENDATION:

OPDRA objects to the approval of the proprietary name Ritalin®-

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

Peter Honig, MD
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

MEDICATION ERROR REVIEW

DATE OF REVIEW: **August 27, 1999**

NAME OF DRUG: **Ritalin®-) (Methylphenidate Hydrochloride Capsule)**

NDA HOLDER: **Novartis**

I. INTRODUCTION:

The Division of Neuropharmacological Drug Products (HFD-120) requested OPDRA evaluate the proprietary name Ritalin®- , manufactured by Novartis for the potential of medication errors due to name confusion.

Ritalin-) is a mild central nervous system (CNS) stimulant. Ritalin presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Ritalin- will be indicated for Attention Deficit Disorder and will be marketed as a once daily formulation of methylphenidate hydrochloride. Ritalin- s an IND and therefore, the container labels, carton and insert labeling were not available for review. The project manager stated this drug product would probably be marketed as a 20 mg capsule.

II. RISK ASSESSMENT:

1. "Ritalin" is an approved proprietary name marketed by Novartis under NDA 10-187 (Ritalin Tablets 5 mg, 10 mg and 20 mg) and NDA 18-029 (Ritalin SR Tablets 20 mg) and therefore,) was the only portion of the proposed proprietary name that was evaluated.

   OPDRA does not recommend the use of in conjunction with the proprietary name Ritalin. is a standard medical abbreviation for . This is a dangerous abbreviation to utilize because it is often misinterpreted as daily when written. Given this proposed once daily formulation of methylphenidate a medication error would result in a overdose.

   Another concern OPDRA had was that multiple prescriptions will be written for the immediate release formulation for children with ADD. The immediate release formulation of Ritalin is often prescribed in different strengths at different times of the day. If "Ritalin is prescribed in addition to the immediate release and misinterpreted as an immediate release the patient will not have the proper coverage for his/her ADD.

An internal study was conducted in OPDRA including 5 individuals. Outpatient prescriptions were written for 2 different drug products (Ritalin — being one of the two) and inpatient orders were written to include Ritalin — The written prescriptions were scanned and e-mailed to the participants. The participants were instructed to respond with their interpretation of what they saw via e-mail. Only one participant interpreted the prescription correctly. All others interpreted the prescription or inpatient order as Ritalin, immediate release tablet, 20 mg daily.

2. There are two commonalties associated with these products. First, all three products have the same proprietary name and secondly, each markets a 20 mg tablet strength. The one major difference between Ritalin and Ritalin SR are the different pharmacokinetics with regards to the onset of action. Ritalin has a peak effect in approximately 4.7 hours and Ritalin SR peaks around 1.9 hours, the excretion is essentially the same. The labeling was not available for the proposed once daily formulation. Because these products have similar strengths and names there is a greater potential for confusion, particularly in the first months after product launch when a new product is not widely recognized. Diltiazem, Diltiazem CD, Diltiazem SR are good examples of this type of confusion. Each having overlapping strengths, same name, and different pharmacokinetics. To help alleviate the confusion each product includes an additional modifier on the container label to differentiate the different dosing recommendations.

3. In addition, we discourage including the dosage regimen in the proprietary name. As the product evolves, newer dosing schedules may be approved which conflict with the information originally contained in the proprietary name.

4. In addition, a handwriting sample was requested from each participant in the study. The handwriting samples did not reveal any look-alike drug products.

OPDRA believes the proposed proprietary name poses a significant risk for potential confusion between the immediate release dosage form of methylphenidate and the proposed once daily formulation. The Agency has always considered the use of coined abbreviations in conjunction with proprietary names objectionable since they can be misinterpreted. We refer you to ASHP Guidelines on Preventing Medication Errors in Hospitals (Am J Hosp Pharm., Vol. 50, Feb 1993), Draft Guidance for Industry on Proprietary Drug Names (May 1999) and The CDER Labeling and Nomenclature Committee, Structure, Function, and Process (Drug Information Journal, Vol. 31, Nov 1997).

RECOMMENDATION:

I. OPDRA objects to the approval of the proprietary name Ritalin — for the reasons cited above.

II. The proposed established name (Methylphenidate Hydrochloride ——— : capsule) is not an approved pharmaceutical dosage form according to the United States Pharmacopeia (USP). The established name of the product should be Methylphenidate Hydrochloride Extended-release Capsules.

III. An additional Modifier should be prominently placed under the established name ———

IV. The SR formulation should also include a modifier " ———

If you have any questions concerning this review please contact Carol Holquist at 301-827-3244.

LS

Carol Holquist, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

LS

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

CC:

Office Files
HFD-120; Kathie Bennett, Safety Evaluator, DDRE I, OPDRA
HFD-430; Min Chen, Team Leader, DDRE I, OPDRA
HFD-430; Peter Honig, Division Director DDRE I, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA

MEMORANDUM

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

DATE: May 14, 2002

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

SUBJECT: Recommendation for Approval Action for
Ritalin LA (— —release methylphenidate) Capsules for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

TO: File NDA 21-284
[**Note:** This overview should be filed with the 10-18-01 response to our 10-1-01 approvable letter.]

We issued an approvable letter for this application on 10-1-01, requesting the following:
-A response to numerous CMC deficiencies.
-A commitment to conduct, postapproval, a juvenile animal study.
-We proposed dissolution specifications, based on bio-batches, beginning at —hours, but asked the sponsor to develop a dissolution specification for the immediate release bead component at an even earlier time point. We rejected the proposed IVIVC.
-We requested additional analyses of weight and vital signs data for studies 7 and 7E.
-We requested a safety update.
-Finally, we included our proposed labeling with the letter.

Novartis initially responded to our letter with a 10-18-01 submission, however, we did not consider this a complete response due to a failure to fully respond to the numerous CMC deficiencies. We detailed these continued deficiencies in an 11-1-01 letter. On 12-6-01, Novartis provided sufficient additional CMC data to consider the response complete. However, it was judged to be a sufficiently complex review to justify a 6-month clock.

CMC:
-The CMC review of the submitted information is complete, and it is my understanding that all remaining issues have been resolved. Thus, the CMC group has recommended approval.

Juvenile Animal Study:
-Novartis indicated in their 10-18-01 response that they have already conducted a juvenile animal study, and would submit the full report in the near future. This has been submitted and reviewed, and, in fact, we have reached agreement with the sponsor on summary information regarding this study for inclusion in labeling.

Dissolution Specifications:
-Agreement has been reached on dissolution specifications as 0f 4-18-02.

Weight and Vital Signs Data:
-Dr. Mosholder reviewed the additional analyses of vital signs and weight data, and indicated that these additional analyses confirmed his earlier finding that, even within the context of a 2-week study, there was a measurable reduction in weight gain for methylphenidate patients compared to placebo. This finding has been noted in labeling.

Safety Update:
-There were no additional safety data to report since the 4-month safety update. As of this time, Ritalin LA is not yet marketed in any country, thus, there are no postmarketing data.

Labeling:
-The labeling issues were relatively minor, and we reached agreement on final labeling as of 5-14-02.
Recommendation: All issues have been resolved, and I recommend that we issue the approval letter included with the approval package, including the mutually agreed upon final labeling for this product.

cc:
Orig NDA 21-284
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/AHomonnay

DOC: MEMRITLA.AP1

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/s/

Thomas Laughren
5/14/02 10:28:28 AM
MEDICAL OFFICER

MEMORANDUM OF TELECON

NDA: 21-284

DRUG: Ritalin LA Extended-release Capsules

SPONSOR: Novartis

DATE: June 5, 2002

TELEPHONE NUMBER: (973) 781-3771

CONVERSATION WITH:

Mara Stiles, Associate Director of Drug Regulatory Affairs
And
Anna Marie H. Weikel, Regulatory Health Project Manager HFD-120

BACKGROUND:
This morning Drs. Katz and Laughren spoke with Mara Stiles about adding a line to the table under 'Dosage and Administration' 'Patients Currently Receiving Methylphenidate' to include information about a 60 mg dose. Mara Stiles said she would check with her group about this change and get back to us.

CONVERSATION:
Mara Stiles called me and said that Novartis has agreed that the following line could be added to the last line of the table:

'30 mg methylphenidate b.i.d. or 60 mg methylphenidate-SR' ..... '60 mg QD'

In addition, she said that Novartis agreed that the suffix 'LA' should be added after Ritalin in the second paragraph on p.11 in the pregnancy section.

Anna Marie H. Weikel, R.Ph.
Regulatory Health Project Manager

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/s/

Anna-Marie Homonnay
6/5/02 02:16:06 PM
CSO

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BRIEF MEETING MINUTES

Date: April 4, 2000

Location: Woodmont II, Conference Room E
Firm: Novartis Pharmaceuticals Corp
Drug: Ritalin® (methylphenidate HCl ; formulation)
Indication: ADHD
Meeting Type: pre-NDA Meeting
Participants:

FDA:
Russell Katz, MD, Division Director
Thomas Laughren, MD, Clinical Teamleader, Psychiatric Drugs
Andrew Mosholder, MD, Clinical Reviewer
Kun Jin, PhD, Teamleader, Biostatistics
Ray Baweja, PhD, Teamleader, Clinical Pharmacology
Ifthekar Mahmood, PhD, Clinical Pharmacology Reviewer
Barry Rosloff, PhD, Pharmacology/Toxicology Reviewer
Anna Marie Homonnay, Regulatory Project Manager

Novartis Pharmaceuticals Corp:
Roy Dodsworth, Drug Regulatory Affairs
Mohammad Hossain, Clinical Pharmacology
Goeril Karlsson, Clinical Research
Elisabeth Koch, Preclinical Safety
Lynn Kramer, Clinical Research
Sabri Markabi, Clinical Research
Dr. Falek, Clinical Research
Harald Pohlmann, Biostatistics
Russell Soma, Pharmaceutical Development
Mara Stiles, Drug Regulatory Affairs

BACKGROUND: This meeting was requested by Novartis in preparation for an NDA submission later this year. The discussion focused on the questions submitted in the March 17, 2000, pre-NDA meeting package (attached).

DISCUSSION:

Clinical Issues:

- FDA raised concerns about the specification of primary outcomes and analyses for Study 02, and whether or not this study could serve as a basis for a claim of effectiveness over a 9 hour time period. As an alternative approach, the sponsor will look separately at AUCs for morning and afternoon. Nevertheless, we indicated that we could not offer a definitive opinion about how we would interpret this study, and that it would be a matter of review.

- FDA indicated that it was apparent there would be no adult data to support dosing recommendations for adults with ADHD, for any formulation of methylphenidate, and that we would take the submission of an NDA for the modified release formulation as an opportunity to clarify in Ritalin labeling that there are no data to address efficacy of methylphenidate in adults with ADHD. We referred to a previous meeting when it was advised that this dosage form be studied in adults.

- FDA suggested that it would be a good idea if Novartis developed a PPI for this drug to go along with the package insert.

- It was agreed that the study groupings proposed for the ISS were acceptable. However, FDA would also want data on withdrawal-emergent adverse events during the placebo wash-out phase. In addition, FDA suggested that the normal values for vital signs and laboratory values be adjusted for the 6-12 age group.

- FDA raised questions about the statistical analysis of Study 02 and requested more details. The statistical analysis of Study 07 was also discussed and more details on the analysis plan were requested.

- FDA said that the studies for the preschool age group may be deferred under the Pediatric Rule.

Clinical Pharmacology Issues:

- Whether the IVIVC will be required upon NDA submission depends upon whether it is critical for setting the dissolution specs, or for biowaivers for other strengths. However, FDA said that the IVIVC may be highly relevant for PK evaluation of the highest strength, 40 mg, in lieu of a comparative study to the IR form.

- It was agreed that the bioequivalence study for the proposed marketed formulation is not necessary and that the dose proportionality study may be waived in lieu of the IVIVC.

- FDA questioned whether the PK of the pediatric age group has been characterized with this dosage form. Novartis responded that this had been the purpose of Study 02.

Pharmacology/Toxicology Issues:

- It was agreed that the proposals for the nonclinical portion, as detailed in the briefing package, were acceptable to FDA.

- FDA also requested that the completed animal reproduction study results be described in the labeling.

Signature, minutes preparer:_____
Anna M. Homonnay-Weikel, RPh
Regulatory Project Manager

Concurrence :_____
Thomas Laughren, M.D.
Clinical Team leader, Psychiatric Drugs

attachment

cc:
HFD-120/orig IND
HFD-120/Laughren
HFD-120/Mosholder
HFD-120/Rosloff

draft: ahw/4.24.00
rev: tl/4.25.00
final: ahw/4.26.00

MEETING MINUTES

MAR 22 2000

BRIEF MEETING MINUTES

Date: March 14, 2000

Location: Woodmont II, Conference Room E
Firm: Novartis Pharmaceuticals Corp.
Drug: methylphenidate HCl modified release formulation
Indication: ADHD
Participants:

FDA:
John Simmons, PhD, ONDC I, Acting Office Director
Bob Seevers, PhD, Chemistry Teamleader, Psychiatric Drugs
Don Klein, PhD, Chemistry Reviewer

Novartis:
Leslie Martin-Hischak
Mara Stiles
Russell Somma
Glenn Thompson
Gurvinder Singh Rekhi
Roy Dodsworth

Elan:
Theresa Chung, Regulatory Affairs

BACKGROUND:
Sponsor requested this pre-NDA CMC meeting in anticipation of an NDA submission for methylphenidate HCl, ——— release capsules around the end of this year. Elan Pharmaceuticals will manufacture the dosage form for Novartis using their SODAS technology. The discussion focused on the two questions (attached) that were submitted in the meeting briefing package dated February 4, 2000, dealing with stability issues.

DISCUSSION:

- There was no objection from FDA regarding the proposed registration stability protocol, including the 5/8 matrix design; however, FDA suggested that the NDA also include two other post-approval stability protocols, one for the first three full scale batches and one for the annual stability batches, in addition to the registration protocol.

- FDA will accept an NDA with 9 months real-time stability data and a 3 month stability update.

- FDA said the stability data from Protocol 02 may support the proposed expiration date for the common strengths provided that the manufacturing process is the same. However, if the manufacturing process differs, than the data will be viewed by FDA as supportive. A different approach, where data is pooled statistically from 3 batches of different strengths which share the same ratios and manufacturing process, may be used to justify the data; however, more batches at the lower strengths would be desirable.

Signature, minutes preparer: /S/

Anna M. Homonnay-Weikel,R.Ph.
Regulatory Project Manager

Concurrence : /S/

Bob Seevers, PhD
Chemistry Teamleader Psychiatric Drugs

cc:

Div Files
HFD-120/Klein
HFD-120/Homonnay

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TELECON MINUTES

Topics for Discussion / Chemistry, Manufacturing and Controls

Drug Product

1. **Registration Stability Protocol**: The registration stability protocol, RSP6032A, for Ritalin- — 20, 30 and 40 mg capsules is provided in Attachment V of this briefing document. The protocol includes a complete description of all batches, packaging configurations, storage conditions, time intervals and tests to be performed to support the registration of Ritalin- — capsules.

The rationale for a proposed ·⅗ matrix design of the room temperature (25°C/60%RH) storage condition is included in the protocol. The ⅗ matrix design studies all batch, strength and package configurations.

Ritalin —capsules are planned for marketing in — bottles with an · — induction seal and child resistent closure.

Does the Agency find the Registration Stability Protocol as presented, including the ⅗ matrix design acceptable for the registration of Ritalin-. — capsule?

2. **Stability**: The ——— formulation in a 10/10 ratio of immediate/delayed release methylphenidate hydrochloride was selected for full development based on results of the clinical study, Protocol 02. The three strengths intended for commercialization are the selected 20 mg (10/10 mg) and two additional strengths of 30 mg (15/15 mg) and 40 mg (20/20 mg). The 30 mg and 40 mg strengths are compositional multiples, maintaining the same ratio of methylphenidate hydrochoride immediate/delayed release content as the selected 20 mg formulation. The three strengths are achieved with different fill levels of the identical formulation..

The method of manufacture of the coated beads for the selected 1 ——— (used in Protocol 02) will remain the same for final development and eventual commercialization of the product. There will be no changes to the process with only an increase in equipment size and scale of manufacture. The commercial equipment has the same design, manufacturer and operating principles.

CLINICAL STABILITY: The — formulation for Protocol 02 was placed on stability in ——— bottles with —— seal, child resistant closure and ——— as well as in bulk ———————) with no ———

REGISTRATION STABILITY: The intended commercial product (20, 30 and 40 mg capsules) has been placed on stability — bottles with an : ———induction seal, child resistent closure and no . They will be tested according to the Registration Stability Protocol RSP6032A.

At the time of NDA filing, nine months (9) months registration stability according to the Registration Protocol, RSP6032A, will be available for three batches of each strength of Ritalin- — capsules. Additionally, there will be twenty-four (24) months, supportive stability for the ——— formulations used in Protocol 02.

A. Will it be acceptable to the Agency to receive a twelve (12) month registration stability update by three (3) months into the review cycle?

B. Will the Agency agree to include the twenty-four (24) month clinical study (Protocol 02) stability data in support of an anticipated request for a two (2) year expiration date for the drug product?

MEETING MINUTES

Date: May 5, 1999

Location: Woodmont II, Conference Room E
Firm: Novartis Pharmaceuticals Corporation
Drug: methylphenidate hydrochloride ; — release formulation
Indication: Attention Deficit Disorder (ADHD)
Meeting Type: Clinical Development Meeting
Participants:

FDA:

Thomas Laughren, M.D.	Teamleader, PDP
Andrew Mosholder, M.D.	Medical Reviewer
Glenna Fitzgerald, Ph.D.	Teamleader, Pharmacology
Barry Rosloff, Ph.D.	Pharmacology Reviewer
Kun Jin, Ph.D.	Teamleader, Biostatistics
Kun He, Ph.D.	Biostatistician
Mahmood Iftekhar, Ph.D.	Clinical Pharmacologist
Anna Marie Homonnay	Project Manager

Novartis:

Roy Dodsworth	Drug Regulatory Affairs
Herbert Faleck	Clinical Research
Kok-Wah Hew	Reproductive Toxicology
Robert Jackson	Project Management
Henry Lau	Clinical Pharmacology
Lynn Kramer	Clinical Research
Sabri Markabi	Clinical Research
Russ Hume	Drug Regulatory Affairs
Rama Seshamani	Medical Affairs
Mara Stiles	Drug Regulatory Affairs
William Sallas	Biostatistics

BACKGROUND:
This meeting was requested by Novartis in order to obtain the Division's input on their proposed clinical development plan for a modified-release formulation of Ritalin^{R}. Novartis plans to market a racemic mixture formulation with a bimodal release pattern which mimics twice daily dosing with Ritalin IR. They already market Ritalin^{R} SR which has a steady flat release profile. They have proposed a development plan consisting primarily of bioequivalence studies.

DISCUSSION:

- The proposed pivotal study, Protocol 02, conducted in a laboratory classroom type setting, would be viewed by the Division as a preliminary supportive study, but not sufficient to be considered pivotal. For external validity, the Division would be prepared to accept one small pivotal efficacy trial conducted on typical ADHD patients in an outpatient setting for approximately three to four weeks duration with DSM-IV criteria as primary endpoints. The use of a failure design, i.e. currently in use for epilepsy and pain trials, for the efficacy study was also discussed. A relapse prevention trial would be useful but not a requirement.

- Seeking approval through the bioequivalence route would be difficult because of the issue of two plasma peaks; however, the Division is willing to review any future bioequivalence proposals. In addition, given that, for this drug, the rate of input may be related to efficacy, the plasma concentration time curves would have to be superimposable for both peaks. There is a concern the the second peak may not meet the IR requirements. In addition, the fluctuation index (including tmax and cmax) should be determined and submitted with all of the other data.

- Labeling for use in adult ADHD should be supported by a single clinical study in adults, not by extrapolation, since the condition is not as well-defined in this population. An IR study may be sufficient for use in the current dose range. However, more open label clinical safety data may be needed for a higher dose range.

- The mouse study performed by NTP appears to satisfy the requirements for a Segment I reproductive study. Novartis's proposal to conduct Segment II and III studies as well as to address the issue of developmental effects in juvenile animals was acknowledged.

ADDENDUM:
Subsequently after the meeting, the Division's concerns about preclinical findings for the proposed excipient, —— _ , were discussed between Drs. Fitzgerald, Rosloff and Dr. Hew. Upon review of the DMF, preclinical studies revealed thyroid hyperplasia, possibly warranting further investigation.

ACTION ITEMS:

- Novartis may work with the Division to finalize the pivotal efficacy protocol.
- Novartis may submit a bioequivalence proposal taking into account the two peak profile of the proposed formulation.
- The safety of the excipient, ——— , should be addressed.

Signature, minutes preparer: _____
Anna M. Homonnay-Weikel,R.Ph.
Project Manager

Concurrence Chair: _____
Tom Laughren, M.D.
Medical Teamleader DPDP

cc:
Orig. — 6-7-99
HFD-120/Laughren
HFD-120/Mosholder/5.13.99 6/7/99
HFD-120/Rosloff/5.13.99
HFD-860/Iftekhar/5.13.99
HFD-120/Homonnay

MEETING MINUTES

MEMORANDUM

DATE: June 5, 2002

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

TO: File, NDA 21-284

SUBJECT: Action Memo for NDA 21-284, for the use of Ritalin LA (methylphenidate HCl) Extended Release Capsules in patients with Attention Deficit-Hyperactivity Disorder (ADHD)

NDA 21-284, for the use of Ritalin LA (methylphenidate HCl) Extended Release Capsules in patients with Attention Deficit-Hyperactivity Disorder (ADHD), was submitted by Novartis Pharmaceuticals Corporation on 11/28/00. The Agency issued an Approvable letter on 10/1/01; the sponsor submitted a complete response to this letter on 12/6/01.

The review team has reviewed this response and recommends that the application be approved. I agree; however, I have one comment for the record.

In the draft labeling accompanying the Approvable letter, we asked the sponsor to draft dosing recommendations for patients naïve to methylphenidate (the controlled trial on which the approvable action was based studied only patients who had previously received methlyphenidate). The sponsor proposed recommendations that the review team has found to be acceptable, and which state that 60 mg is the maximum recommended dose in these patients. The recommendations included in our draft labeling for patients already receiving methylphenidate implied that 40 mg was the maximum recommended dose (this was the maximum dose studied in the controlled trial). Two issues are raised by these statements.

First, 60 mg of Ritalin LA has never, to my knowledge, been studied, either in naïve, or previously treated, patients. The sponsor's choice of 60 mg as the recommended maximum dose in naïve patients was based on the fact that the maximum recommended dose of immediate release Ritalin is 60 mg/day, given in divided doses, and that in the controlled trial, patients' daily immediate release methylphenidate dose (given either twice a day, or once a day in an SR preparation) was replaced by the same daily dose of Ritalin LA, given once/day. Given this mg for mg replacement of immediate release (or SR) methylphenidate with the same dose of Ritalin LA in the controlled trial, it is reasonable, in my view, to expect that Ritalin LA, at the highest daily dose recommended for immediate release Ritalin, will be effective. Further, there are no immediate safety concerns raised by a 60 mg dose of Ritalin LA, as it will result in a Cmax that is lower than that achieved after Ritalin immediate release, given as 30 mg

BID. For these, reasons, I believe it is reasonable to permit a recommendation for the 60 mg dose of Ritalin LA (note that this does not presuppose that a 60 mg dose of Ritalin LA is equi-effective to a Ritalin dose of 30 mg BID; only that the former would be expected to be effective, given that Ritalin LA is effective at doses up to the maximum studied dose of 40 mg once a day, and that Ritalin is effective at 30 mg BID).

We will also amend the dosing recommendations for patients who have previously been treated with methylphenidate, to include instructions for transferring patients from IR (or SR) doses of 60 mg/day to 60 mg once/day of Ritalin LA (given the above considerations, there is no reason to limit the dose in these patients to the maximal dose of 40 mg/day used in the controlled trial).

For these reasons, and with these changes to labeling, I will issue the attached Approval letter.

Russell Katz, M.D.

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/s/

Russell Katz
6/5/02 12:49:11 PM
MEDICAL OFFICER

MEMORANDUM

DATE: September 27, 2001

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

TO: File, NDA 21-284

SUBJECT: Action Memo for NDA 21-284, for the use of Ritalin LA (methylphenidate HCl extended release capsules) for the treatment of patients with Attention Deficit Hyperactivity Disorder (ADHD)

NDA 21-284, for the use of Ritalin LA (methylphenidate HCl extended release capsules) for the treatment of patients with Attention Deficit Hyperactivity Disorder (ADHD), was submitted by Novartis Pharmaceutical Corporation on 11/28/00. The application contains the results of 2 randomized controlled trials (Studies 07 and 02), as well as CMC and pharmacokinetic data.

The application has been reviewed by Dr. Andrew Mosholder, medical reviewer, Dr. Kallapa Koti, statistician, Dr. Gurpreet Gill-Sangha, chemist (review dated 8/17/01), Dr. Ronald Kavanagh, Office of Clinical Pharmacology and Biopharmaceutics (review dated 9/7/01), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 9/17/01).

The clinical review team has concluded that the data establish the safety and effectiveness of Ritalin LA when given once a day. I agree. I also agree that the primary trial on which this conclusion is based is Study 07, a parallel group outpatient study. Of course, the conclusion is in turn based on the existing data for Ritalin IR, the previously approved immediate release product.

However, as Drs. Gill-Sangha and Laughren note, the Agency has previously concluded that there were serious laboratory and data integrity problems at the site of manufacture, testing, and packaging of the drug product (Elan Holdings, GA). While the problems were not necessarily noted in the production of Ritalin LA, they were noted to have occurred in the production of another drug which utilized identical processes to those used for Ritalin LA. Elan is currently under a Consent Decree, and the Office of Compliance has recommended that the application not be approved until a subsequent inspection determines that the problems have been resolved. I have spoken with Dr. Robert Seevers, Chemistry Team Leader, who has learned from the Office of Compliance, that the company requested a re-inspection about 2 weeks ago.

Given the fact that the Agency has no independent evidence that the critical data integrity problems have been resolved, we must consider the deficiencies unresolved. I believe that the nature of these particular deficiencies is sufficiently

serious that it would ordinarily be appropriate to issue a Not Approvable letter. While I acknowledge that the sponsor has requested a re-inspection, implying that they believe the issues have been adequately addressed, in my view this provides no evidence, even in a preliminary way, that the problems have been resolved.

However, the Agency did issue a memo to the sponsor, signed by Betty J. Jones, Deputy Director, Office of Compliance, dated 6/25/01, which clearly states that, "at this time", the plant is in compliance with current Good Manufacturing Practices (cGMP). This memo was issued in response to a request from the company to the Agency for documentation that they were in compliance with cGMP. This request was intended to obtain documentation that could be sent to European regulators (according to the company, they were under the impression at the time of their request [6/18/01] that they were in compliance, presumably based on conversations they had had with the Agency's district office). I have discussed this with Dr. Seevers, who has discussed this with Ms. Jones. In actuality, this memo (and presumably other communications from the district office to the sponsor) misstates the Agency's current view of the situation; that view, as explained above, is that we cannot consider the company to be in compliance until a re-inspection has been performed, and we have determined that the problems have been resolved.

While, as I noted earlier, I would ordinarily issue a Not Approvable letter given the unresolved serious deficiencies, it is clear that, inadvertently, the Agency's 6/25 memo (and other communications) probably misled the sponsor into thinking that many of the issues had been resolved (this, for example, could explain why the sponsor did not request a re-inspection sooner than they did).

In any event, given this sequence of events, I will issue an Approvable letter. The letter will make clear that the application may not be approved until a satisfactory inspection has been performed.

Russell Katz, M.D.

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/s/

Russell Katz
10/1/01 12:35:12 PM
MEDICAL OFFICER