CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-284

CORRESPONDENCE

Desk copy: Ms. A. Homonnay-Weikel

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

May 13, 2002

NDA 21-284
Ritalin® LA
(methylphenidate hydrochloride)extended-release capsules

Russell Katz, MD
Director
Division of Neuropharmacological Drug Products
HFD-120
Center for Drug Evaluation and Research
Attention: Ms. Anna Marie Homonnay-Weikel
1451 Rockville Pike
Rockville, MD 20857

Dear Dr. Katz:

Please refer to our pending NDA 21-284 for Ritalin LA and also to the FDA final labeling proposal faxed May 9.

This is to provide our agreement with the final proposed labeling with the inclusion of the following three changes which are found on pages 1,5, and 16 of the May 9 fax.

Page1: Add back into Description section previously proposed sentence identifying SODAS. Per telephone contact with Project Manager Ms. Anna Marie Homonnay-Weikel on May 10, we understand that it is acceptable to include this in the labeling.

Page 5: Add back into Food Effects section "concentration and the extent of absorption" into the second sentence of the second paragraph as was stated in the FDA labeling proposal sent on April 12, 2002:

With this return to previous text the sentence would read as follows: The first peak concentration and the extent of absorption was unchanged after food relative to the fasting state, although the second peak was approximately 25% lower.

Page 16: Add back into How Supplied section the refernce to trademark ownership for Ritalin LA and SODAS.

For any questions or comments regarding this submission, please contact me at (973) 781-3771.

Sincerely,

Mara Stiles

Mara Stiles
Associate Director
Drug Regulatory Affairs

3 pages redacted from this section of the approval package consisted of draft labeling

MODE = MEMORY TRANSMISSION START=MAY-09 17:32 END=MAY-09 17:43

FILE NO.= 244

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	#	919737817177	022/022	00:10'05"

-FDA/DNDP -

********** -FDA/DNDP - ***** - 301 594 2858- **********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: May 9, 2002

To: Mara Stiles

Company: Novartis Inc.

Fax number: (973) 781-7177

Phone number:

From: Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager
Division of Neuropharmacological Drug Products

Fax number: (301) 594-2859

Phone number: (301) 594-5535

Subject:

Total no. of pages including cover:

Mara,

Please find the FDA final labeling proposal. We are willing to further discuss if needed. Please give me a call.

Thanks,

Anna Marie

Document to be mailed: ☐ YES ☑ NO

21 pages redacted from this section of the approval package consisted of draft labeling

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:	NDA Letter
Document Group:	Approvable Letters
Document Name:	Approvable letter - Misc. deficiencies and labeling revisions listed in letter.
Letter Code:	NDA-H4
COMIS Decision:	AE: APPROVABLE
Drafted by:	ahw/September 28, 2001
Revised by:	TL/10.1.01
Initialed by:	
Finalized:	
Filename:	C:\wpfiles\NDA\RitalinLA\21284AEltrwlab.doc
DFS Key Words:	
Notes:	
Linking Instructions:	If this is the first action on the application, link the outgoing letter to the N, RS, AR, or FO coded incoming document, as appropriate. Otherwise, the outgoing letter must be linked to the major amendment submitted in response to the previous action letter. In addition, the outgoing document should also link to all associated amendments and correspondences included in the action. Do NOT link this letter to any amendments that were not reviewed for this review cycle (i.e., amendments where the review was deferred to the next review cycle).

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

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/s/

Russell Katz
10/1/01 12:38:06 PM

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:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Information request letter for a pending NDA
Shortcut ID Code:	NDA-E1
COMIS Decision:	IR (INFORMATION REQUEST)
COMIS Data Entry:	
Drafted by:	ggs/April 1, 2002
Revised by:	
Initialed by:	
Finalized:	
Filename:	C:\Data\My Documents\data ggill\NDA\21284\IR_ltr4102.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-284

INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation
Attention: Elizabeth McCartney
Assistant Director, Drug Regulatory Affairs
One Health Plaza
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. McCartney:

Please refer to your December 6, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ritalin® LA (Methylphenidate HCl modified release) Capsules 20, 30 and 40 mg.

We also refer to your submissions dated October 18, 2001 and February 28, 2002.

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. The Table of Composition of the Ritalin LA (Vol. 1.3, page 4-41, Table 4-1 of the original submission) as presented does not provide detailed information on individual composition of IR and DR beads for each dosage strength. Please provide the updated Table of Composition to reflect the composition of the IR and DR beads for each dosage strength.

2. Please provide the updated drug product specifications for Ritalin LA including the changes in the related substances specifications. The dissolution specifications for the drug product should be incorporated as per agreement with the Agency's biopharm division and Novartis.

3. Please provide the updated specifications for the IR and DR beads including the revisions in the related substance specifications as per your acknowledgement dated December 6, 2001.

4. The [redacted] were never used in any Ritalin LA stability studies as per the October 18, 2001 amendment in response to Q9 in the FDA approvable letter dated October 1, 2001. These packaging components should therefore not be used for the commercial product unless acceptable stability data supporting their use for the drug product packaging is provided.

5. A 24 month expiry for Ritalin LA is acceptable based on the 24 month real time data. We also acknowledge that the stability specifications are the same as the approved regulatory specifications at release as per the February 28, 2002 amendment.

If you have any questions, call Anna Marie Homonnay, Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

Hasmukh B. Patel, Ph.D.
Acting Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Hasmukh Patel
4/3/02 02:33:41 PM

MODE = MEMORY TRANSMISSION START=APR-03 14:54 END=APR-03 14:55

FILE NO.= 051

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	919737816325	004/004	00:01'00"

-FDA/DNDP -

********** -FDA/DNDP - ***** - 301 594 2858- **********

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I

FACSIMILE TRANSMITTAL SHEET

DATE: April 3, 2002

To: Betsy McCartney

Company: Novartis

Fax number: (973) 781-6325

Phone number: (973) 781-8391

Subject:

Total no. of pages including cover: 4

FDA Information Request Letter for NDA 21-284

From: Anna Marie Homonnay, R.Ph.
Regulatory Health Project Manager
Division of Neuropharmacological Drug Products
Fax number: (301) 594-2859
Phone number: (301) 594-5535

Document to be mailed: ☐ YES ☑ NO

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:	NDA Letter
Document Group:	Acknowledgement Letters
Document Name:	Acknowledge COMPLETE response to an action letter
Letter Code:	NDA-A3
COMIS Decision:	No Decision Code *(RESUBMISSION ACKNOWLEDGMENT)*
Drafted by:	ahw/December 13, 2001
Revised by:	
Initialed by:	Seevers/12.13.01/Laughren/12.13.01
Finalized:	Ahw/12.13.01
Filename:	Wpfiles/NDA/RitalinLA/21284ACKCR.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link the outgoing letter to the single incoming document that completes the response to the action letter. This incoming document should be coded a major amendment. If this incoming document is coded a correspondence (i.e., C) or a minor amendment (e.g., BM, BC, etc.), then the amendment type code for this incoming document must be changed by the document room staff to a major amendment prior to submitting this letter into DFS. Any previous amendments that were submitted in response to the action letter but were considered incomplete responses should be code as either minor amendments or correspondences (C).

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-284

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936

Dear Ms. Stiles:

We acknowledge receipt on October 19, 2001, of your October 18, 2001, submission to your new drug application (NDA) for Ritalin® LA (methylphenidate hydrochloride) extended-release capsules.

We refer to the October 11, 2001, teleconference between FDA and representatives of Novartis during which the CMC issues raised in our action letter were clarified and the format for the analytical methods section was discussed.

We also refer to your October 30, 2001, facsimile.

This submission contains additional chemistry, pharmacology/toxicology, biopharmaceutics and clinical information submitted in response to our October 1, 2001 action letter.

We do not consider this a complete response to our action letter. Therefore, the review clock will not be started until we have received a complete response. The following deficiencies from our action letter still need to be addressed:

1. **Response to FDA CMC Q3:** We note that in the table of contents in the faxed response to FDA Q6, the dissolution specifications for the DR beads are provided on page 68 of the resubmission and you imply that these are the dissolution specifications for the DR beads. You had responded in the earlier resubmission dated October 18, 2001 that the DR bead specifications for the in-process controls would be provided after NDA approval, which is unacceptable. There is still no batch data for the IR or DR beads in-process specifications. In order for a complete response to the FDA approvable letter, please provide the following:

   • Confirm the DR dissolution specifications provided on page 68 of the resubmission are the same as that of the in-process dissolution specifications for the DR beads.

   • Provide data on 3 batches of IR and DR beads in-process specifications including the tests, acceptance criteria limits and the batch results.

2. **Response to FDA CMC Q6:** We refer to your fax submission dated October 30, 2001 containing the completed table of contents with page numbers which were missing from the original resubmission. As you acknowledge in the original resubmission, the re-presentation of the information may not completely address the FDA concerns raised in the approvable letter and teleconference dated October 11, 2001. It is also not appropriate to refer to the Agency 2000 draft guidance on analytical procedures and methods validation because it is a draft guidance. In addition, this guidance does not address format, which is specifically the concern in your resubmission. In order to satisfactorily and completely respond to Q6 of the FDA approvable letter, you must explicitly provide the following:

   • Details of each analytical method individually, including, specific assay method, impurity profile by HPLC, dissolution method, etc.

   • Each individual method must be provided in a single coherent text with the following information:

   1. A final method code for each method
   2. Specifications
   3. Sampling plan
   4. Detailed analytical method

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
11/1/01 09:11:00 AM

SEP 30 1999

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
59 Route 10
East Hanover, NJ 07936-1080
Attention:

Dear Ms. Stiles:

Reference is made to your [redacted] for modified- release methylphenidate hydrochloride and your submission dated August 19, 1999.

We have completed our review of your protocols for Protocol Summary 07 and have the following comments:

1. The study design would be improved in either version by the addition of a standard Ritalin arm for comparison.

2. The interpretation of the treatment failure design study may be confounded by possible withdrawal effects,since the placebo patients will be discontinuing from methylphenidate. An acute treatment design, in which subjects are medication free at baseline, and then randomized to active drug or placebo for several weeks would be more appropriate.

3. Please note that statistical analysis plans must be provided in detail in order for us to render a complete opinion on any proposed pivotal trial.

In addition, we would like to provide you with feedback obtained from the Office of Post-Marketing Drug Risk Assessment (OPDRA) regarding the proposed trademark, Ritalin [redacted]

OPDRA does not favor the use of [redacted] in conjunction with the proprietary name Ritalin® since [redacted] is a standard medical abbreviation for [redacted] and may be confused in clinical practice with the immediate release product with the same proprietary name as well as with the medical abbreviation, [redacted], for [redacted].

If your should have any questions regarding these comments, please contact Ms. Anna M. Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely yours,

RS

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
IND Orig
HFD-120
HFD-120/Katz 9-24-99
/Laughren
/Mosholder/9.22.99 9/24/99
/Homonnay

C:\WPFILES\IND\ADHD\RITALIN\

ADVICE

Homonnay

MAR 22 2000

Novartis Pharmaceuticals Corporation
Attention: Leslie Martin-Hischak
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Martin-Hischak:

Please refer to the teleconference between representatives of your company and FDA on March 14, 2000. The purpose of the meeting was to discuss the Chemistry, Manufacturing and Controls issues for a proposed NDA for modified release Ritalin.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting.

If you have any questions, contact Anna Marie Homonnay-Weikel, R.Ph., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

3/22/00

Bob Seevers, PhD
Chemistry Teamleader, Psychiatric Drugs
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Orig IND
HFD-120/Klein
HFD-120/Homonnay

GENERAL CORRESPONDENCE (MINUTES SENT)

Homonnay

JUN 17 1999

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
59 Route 10
East Hanover, NJ 07936-1080

Dear Ms. Stiles:

Please refer to the meeting between representatives of your firm and FDA on May 5, 1999. The purpose of the meeting was to obtain input on your proposed clinical development plan for a modified-release formulation of Ritalin^{R} (methylphenidate hydrochloride) Tablets.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

We also acknowledge receipt of your May 28, 1999, minutes of the meeting.

If you have any questions, contact Anna M. Homonnay-Weikel, R.Ph., Project Manager, at (301) 594-5535.

Sincerely,

/S/

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-284

Novartis Pharmaceuticals Corporation
Attention: Mara Stiles
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936

Dear Ms. Stiles :

We acknowledge receipt on December 7, 2001, of your December 6, 2001, resubmission to your new drug application for Ritalin® LA (methylphenidate hydrochloride) Extended-release Capsules.

We also refer to our November 1, 2001, letter outlining the deficiencies in your October 18, 2001, submission.

We consider this a complete Class 2 response to our October 1, 2001, action letter; therefore, the user fee goal date will be June 7, 2002.

If you should have any questions, please call Ms. Anna Marie Homonnay, R.Ph., Regulatory Health Project Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
1/2/02 02:55:16 PM

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pages of trade secret and/or confidential commercial information

MEMORANDUM

Date: January 14, 2002

To: Thomas Laughren, MD
Deputy Director
Division of Neuropharmacologic Drug Products
HFD-120

From: Lisa Stockbridge, Ph.D.
Regulatory Reviewer
Division of Drug Marketing, Advertising, and Communications
HFD-42

Re: Review of Methylphenidate Patient Package Insert

I have reviewed the Patient Package Inserts (PPI) for approved methylphenidate drug products and the proposed PPI for Ritalin LA. I recommend that the following template be adopted for each methylphenidate drug product:

PATIENT LABELING

TRADENAME
(generic name)

Read this information before you start taking TRADENAME (TRADE-name). Also, read the information you get each time you renew your prescription, in case anything has changed. This information does not take the place of your doctor's instructions. If you have any questions about this information or about TRADENAME, talk to your doctor or pharmacist.

What is the most important information I should know about TRADENAME?

Abuse of TRADENAME can cause addiction. Abusing TRADENAME can cause abnormal thinking and behavior. It is important to tell your doctor if you have ever abused drugs or alcohol so your doctor can decide if TRADENAME is right for you.

What is TRADENAME?

TRADENAME is a once-a-day treatment for Attention Deficit Hyperactivity Disorder (ADHD). TRADENAME contains the stimulant methylphenidate. Your doctor has prescribed this medicine as part of an overall treatment plan to control your symptoms of ADHD. TRADENAME has not been studied in children under 6 years old.

[*For appropriate brands*] The TRADENAME capsule dissolves right after you swallow it in the morning, giving you a dose of methylphenidate right away. The rest of the methylphenidate is slowly released during the day to continue controlling your ADHD.

Who should not take TRADENAME?

Do <u>not</u> take TRADENAME if you

- have uncontrollable anxiety, tension, or nervousness. TRADENAME may make these symptoms worse.
- have glaucoma, an eye disease
- have motion tics (hard-to-control, repeated twitching of any parts of your body), verbal tics (hard-to-control repeating of sounds or words)
- have Tourette's Syndrome, or if people in your family have Tourette's Syndrome
- take monoamine oxidase inhibitors (MAOI), a type of medicine used for depression and other mental problems
- are allergic to methylphenidate or any of the other ingredients in TRADENAME. If you need to know the inactive ingredients, ask your doctor or pharmacist.

TRADENAME can make some conditions worse. **Talk to your doctor <u>before</u> taking TRADENAME if you**

- are being treated for depression or have symptoms of depression, such as feelings of sadness, worthlessness, and hopelessness
- have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis
- have had seizures (convulsions, epilepsy) or abnormal EEG's (electroencephalograms)
- have high blood pressure

Tell your doctor right away if you develop any of the above conditions or symptoms while taking TRADENAME.

Tell your doctor if you are

- **pregnant or plan to become pregnant**. We do not know if TRADENAME can harm your unborn baby.
- **breast-feeding**. We do not know if TRADENAME can pass through your milk and harm the baby.

Tell your doctor about all medicines you are taking or plan to take, including prescription and non-prescription medicines and supplements. Your doctor will decide if you can take TRADENAME with your other medicines.

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

How should I take TRADENAME?

For Concerta:

- Take CONCERTA once a day in the morning, with or without food.
- Do not chew, crush, or divide it. Swallow it whole with liquids.

For Metadate CD:

- Take METADATE CD once a day in the morning before breakfast.
- Do not chew, crush, or open the capsule. Swallow it whole with liquids.

For Metadate ER, Methylin ER, and Ritalin SR:

- For Adults and Children:
  - Swallow [TRADENAME] whole. Do not chew or crush it.

For dexmethyl phenidate:

- Take dexmethyl phenidate 2 times a day, at least 4 hours apart, with or without food.

For Metadate immediate release (in Metadate ER PI), Methylin (in Methylin ER PI), and Ritalin (in Ritalin SR PI):

- *For Adults:*
  - Take [TRADENAME] in divided doses, 2-3 times a day. If possible, take it 30-45 minutes before meals.
  - If you have trouble sleeping, take the last dose before 6 p.m.
- *For Children:*
  - Take [TRADENAME] 2 times a day, before breakfast and lunch.

For all:

- Take the dose prescribed by your doctor. Your doctor may adjust your dose until it is right for you. From time to time, your doctor may stop your treatment to check your symptoms while you are not taking the medicine.
- If you take more than the prescribed dose of TRADENAME, tell your doctor right away or call the Poison Control Center in your area.

What are the possible side effects of TRADENAME?

The most common side effects of TRADENAME are

- headache
- stomach pain
- trouble sleeping
- decreased appetite

Other common side effects are nausea, vomiting, dizziness, nervousness, tics, allergic reactions, increased blood pressure, and psychosis. Psychosis is abnormal thinking or seeing or hearing things that are not there (hallucinations).

Weight gain and growth may be slowed in children who use TRADENAME for a long period of time.

Tell your doctor right away if you develop blurred vision. This can be a sign of a serious problem.

This is not a complete list of possible side effects. Ask your doctor or pharmacist about these and other side effects. Talk to your doctor if you develop any side effects that concern you.

General advice about TRADENAME

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use TRADENAME for a condition for which it was not prescribed. Do not give TRADENAME to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about TRADENAME. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about TRADENAME that is written for health professionals. You can also call 1-800-.... or see the TRADENAME website at www. .....

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/s/

Lisa Stockbridge
1/14/02 02:18:41 PM
CSO