CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-259

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

The Office of Clinical Pharmacology and Biopharmaceutics proposes the following labeling text for the proposed paragraph revisions:

METADATE CD was administered as repeated once-daily doses of 20 mg or 40 mg to children aged 7-12 years with ADHD for one week. After a dose of 20 mg, the mean (±SD) early C_{max} was **8.5 (±2.1)**, ng/mL, the later C_{max} was **10.9 (±3.9)*** ng/mL and AUC_{0-9h} was 63.0 (±16.8) ng.h/mL. The corresponding values after a 40 mg dose were **16.8 (±5.1)** ng/mL, **15.1 (±5.8)*** ng/mL and 120 (±39.6) ng.h/mL, respectively. The early peak concentrations (median) were reached about **1.5** hours after dose intake, and the second peak concentrations (median) were reached about **4.5** hours after dose intake. The means for C_{max} and AUC following a dose of 20 mg were slightly lower than those seen with 10 mg of the immediate-release formulation, dosed at 0 and 4 hours.

*25-30% of the subjects had only one observed peak (C_{max}) concentration of methylphenidate

CELLTECH

Facsimile

To:	Ms. Anna Marie Homonnay-Weikel
Company:	FDA, Division of Neuropharmacological Drug Products
Fax number:	301-594-2858
From:	Norma J. Cappetti
Date:	March 19, 2001
Subject:	NDA 21-259 Metadate CD Labeling
Total number of pages:	6

Anna Marie,

In response to our teleconference of March 14, 2001 we are providing the requested plasma concentration listings from study MAI 1001-02 in which the peak plasma concentrations have been identified by the fixed time periods of 0-3hrs and 4.5-9hrs in Microsoft Excel format. On the attached spreadsheets, a box has been drawn around the highest plasma concentrations within each time period. A plasma concentration which has been double underlined indicates the highest concentration for those subjects having only one peak. Separate listings are also provided in which the actual 1st and 2nd peaks have been identified irrespective of the constraint of artificial time periods. The following listings and tables are provided:

- Table 1: Summary table presenting arithmetic mean ± SD, median, minimum and maximum t_{max} data for 20 mg and 40 mg dose strengths from all attached spreadsheets
- Microsoft Excel spreadsheets for the 20mg and 40mg dose groups where the peak concentrations are identified within the fixed intervals of 0-3 hrs and 4.5-9.0 hrs
- Microsoft Excel spreadsheets for the 20mg and 40mg dose groups where the actual peak concentrations are identified (irrespective of the constraint of specific time intervals as in above)

With only one exception, the median times to 1st and 2nd peaks are consistently 1.5 and 4.5 hrs respectively. We therefore accept and support the suggestion made by the Agency March 14 to include median data in the labeling and request approval of the following sentence in the Absorption and Distribution subsection of the labeling:

[ ]

Thank you for the consistently expeditious review time which has occurred for this application to date. We look forward to reaching rapid agreement on text for this remaining label statement.

Sincerely,

Norma J. Cappetti

Celltech Americas, Inc. Regulatory Affairs
755 Jefferson Road Rochester, NY 14623
P.O. Box 31710 Rochester, NY 14603-1710
Tel: 716-274-5828 Fax: 716-272-3952 E-Mail: norma.cappetti@celltechgroup.com

TABLE 1

	Time to Peak Concentrations Within Fixed Time Periods of 0-3 and 4.5-9hrs				Time to Peak Concentrations Based on Actual 1st & 2nd Peaks			
	Excluding Patients with One Peak		All Patients		Excluding Patients with One Peak		All Patients	
t_{max}	1st	2nd	1st	2nd	1st	2nd	1st	2nd*
Mean±SD 20mg	2.1 ± 0.7	5.3 ± 1.1	2.2 ± 0.7	5.1 ± 1.0	1.6 ± 0.2	4.3 ± 1.2	1.9 ± 0.9	4.3 ± 1.2
Mean±SD 40mg	2.0 ± 0.7	4.8 ± 0.6	2.2 ± 0.9	5.0 ± 0.8	2.0 ± 1.2	5.0 ± 2.3	2.9 ± 2.1	5.0 ± 2.3
Median 20 mg	1.5	4.5	1.75	4.5	1.5	4.5	1.5	4.5
Median 40 mg	1.5	4.5	2.25	4.5	1.5	4.5	1.5	4.5
Range 20 mg	—	—	—	—	—	—	—	—
Range 40 mg	—	—	—	—	—	—	—	—

* Data based on patients having two peaks are presented.

USING FIXED TIME PERIODS: 20 mg
Study MAI 1001-02 Plasma Levels 30:70 Ratio

	Time (hours)										Max	Max
SUBJECT	0	0.5	1.5	2	3	4.5	6	7.5	9		0-3 hours	4.5-9
4											1.5	4.5
5											3	6
11											2	6
12											1.5	4.5
14											3	4.5
18											1.5	7.5
27											1.5	4.5
31											1.5	4.5
35											3	4.5
42											3	6
44											3	4.5
46											1.5	4.5

Excluding one peak			Including one peak	
	tmax	tmax	tmax	tmax
	0-3	4.5-9	0-3	4.5-9
	1.5	4.5	1.5	4.5
	1.5	4.5	1.5	4.5
	1.5	4.5	1.5	4.5
	1.5	4.5	1.5	4.5
	1.5	4.5	1.5	4.5
	2	6	1.5	4.5
	3	6	2	4.5
	3	6	3	4.5
	3	7.5	3	6
			3	6
			3	6
			3	7.5
Arithmetic mean	2.1	5.3	Arithmetic mean 2.2	5.1
STDEV	0.7	1.1	STDEV 0.7	1.0
Min	1.5	4.5	Min 1.5	4.5
Max	3	7.5	Max 3	7.5
Median	1.5	4.5	Median 1.75	4.5

USING FIXED TIME PERIODS: 40 mg

Study MAI 1001-02 Plasma Levels 30:70 Ratio

	Time (hours)									Max	Max
SUBJECT	0	0.5	1.5	2	3	4.5	6	7.5	9	0-3 hours	4.5-9 hours
1										1.5	4.5
3										3	6
10										3	4.5
15										1.5	4.5
16										3	4.5
28										1.5	6
36										1.5	4.5
37										3	6
47										3	4.5
32											
39										0.5	exclude

Exduding one peak			Including one peak	
	tmax 0-3	tmax 4.5-9	tmax 0-3	tmax 4.5-9
	1.5	4.5	0.5	
	1.5	4.5	1.5	4.5
	1.5	4.5	1.5	4.5
	1.5	4.5	1.5	4.5
	3	4.5	1.5	4.5
	3	6	3	4.5
			3	4.5
			3	6
			3	6
			3	6
Arithmetic mean	2	4.8	2.2	5.0
STDEV	0.7	0.6	0.9	0.8
Min	1.5	4.5	0.5	4.5
Max	3	6	3	6
Median	1.5	4.5	2.25	4.5

USING ACTUAL 1ST AND 2ND PEAK DATA: 20 mg
Study MAI 1001-02 Plasma Levels 30:70 Ratio

	Time (hours)									Time to	Time to
SUBJECT	0	0.5	1.5	2	3	4.5	6	7.5	9	1st peak	2nd peak
4										1.5	4.5
5										1.5	3
11										2	6
12										1.5	3
14										4.5	
18										1.5	3
27										1.5	4.5
31										1.5	
35										3	
42										1.5	6
44										1.5	4.5
46										1.5	4.5

Excluding one peak		
	Time to 1st peak	Time to 2nd peak
	1.5	3
	1.5	3
	1.5	3
	1.5	4.5
	1.5	4.5
	1.5	4.5
	1.5	4.5
	1.5	6
	2	6
Arithmetic mean	1.6	4.3
STDEV	0.2	1.2
Min	1.5	3
Max	2	6
Median	1.5	4.5

Including one peak	
	Time to 1st peak
	1.5
	1.5
	1.5
	1.5
	1.5
	1.5
	1.5
	1.5
	1.5
	2
	3
	4.5
Arithmetic mean	1.9
STDEV	0.9
Min	1.5
Max	4.5
Median	1.5

USING ACTUAL 1ST AND 2ND PEAK DATA : 40 mg
Study MAI 1001-02 Plasma Levels 30:70 Ratio

SUBJECT	Time (hours) 0	0.5	1.5	2	3	4.5	6	7.5	9	Time to 1st peak	Time to 2nd peak
1										1.5	4.5
3										6	
10										4.5	9
15										1.5	3
16										4.5	
28										1.5	6
36										1.5	4.5
37										6	
47										1.5	3
32											
39										0.5	

Excluding one peak	Time to 1st peak	Time to 2nd peak
	1.5	3
	1.5	3
	1.5	4.5
	1.5	4.5
	1.5	6
	4.5	9
Arithmetic mean	2	5
STDEV	1.2	2.3
Min	1.5	3
Max	4.5	9
Median	1.5	4.5

Including one peak	Time to 1st peak
	0.5
	1.5
	1.5
	1.5
	1.5
	1.5
	4.5
	4.5
	6
	6
Arithmetic mean	2.9
STDEV	2.1
Min	0.5
Max	6
Median	1.5

WITHHOLD 21 PAGE (S)

/s/

Russell Katz
2/2/01 10:37:22 AM

WITHHOLD 1 PAGE (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-259

DISCIPLINE REVIEW LETTER

Medeva Pharmaceuticals, Inc
Attention: Norma J. Cappetti
Director Regulatory Affairs
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710

Dear Ms. Cappetti:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADEMARK ™ (Methylphenidate Hydrochloride USP) capsules.

We also refer to your submissions dated December 15, 2000 and December 26, 2000.

Our review of the Chemistry section of your submissions is complete, and we have identified the following deficiencies:

1. We remind you that your drug substance DMF (——) remains deficient. Please note that approval of your NDA is contingent upon a satisfactory response to our 12/07/00 deficiency letter regarding this DMF.

2. Your proposed specifications for the extended release beads include 1, 2, 4, and 12 hour dissolution testing time points, whereas the results reported on pages 123-125 of V2 in the NDA report include only the 1 and 12 hour time points. Please provide the missing release testing dissolution data for these 3 batches (batches EA-623, EA-626 and PE104EA-630) of ER beads. We note the related bead stability data presented on page 140 of V2.

3. The proposed 12 hour dissolution specification for the ER beads is —— %. However, the 12 hour dissolution performance for the aforementioned batches is greater than —— %. Please tighten this specification (e.g., —— %) so that it is based on and reflective of the data.

4. The certificates of analysis for the release testing of drug product batches EA604, EA688 and EA-689 are missing the 2 hour and 8 hour dissolution time points. Please explain this discrepancy and provide the missing data if available.

5. We acknowledge your commitment in the original submission to place the first three marketed lots of drug product into the approved "marketed product stability program".

Food and Drug Administration
Rockville MD 20857

6. We acknowledge your December 15, 2000 intention to not market the ——— package presentation at this time.

7. Please tighten the 4 hour (e.g., — %) and 12 hour (e.g., — 85%) drug product dissolution specifications so as to be more reflective of the release and stability data provided.

8. The following comment is not an approvable issue and requires no response from you at this time. Although within your proposed specifications, we note that the drug product moisture content increases approximately om initial by 18 months at 25C/60%RH for the batches packaged at —— For those batches packaged at ——— the change in water content is negligible (at 24 months at 25C/60%RH). While this does not appear to impact on drug product safety at this time, we do recommend that you ascertain the reason(s) for this currently uncontrolled difference in quality.

9. Once final test methods and specifications are agreed to, please submit an updated Methods Validation Package.

10. In the text of your proposed storage statement, please change "(77°)" to (77°F).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Anna Marie Homonnay, R.Ph., Regulatory Management Officer, at (301) 594-5535.

Sincerely,

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Robert H. Seevers
12/28/00 04:04:10 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 10 2001

Homonnay

Medeva Pharmaceuticals
Attention: Diane Peterson, Ph.D.
Vice President
3501 W. Garry Avenue
Santa Ana, CA 92704

Dear Dr. Peterson:

Your letter dated December 29, 2000, authorizes us to reference Drug Master File (DMF) ——— for Methylphenidate Hydrochloride, USP drug substance manufacture in support of your new drug application (NDA 21-259).

We have reviewed your communication dated December 29, 2000 in response to our December 12, 2000 deficiency letter and it is deficient. Since approval of your NDA is contingent upon adequate information being provided in this supporting DMF, please address the following issue as soon as possible.

As currently worded, your December 29, 2000 proposed specification of ——— % for Total other Impurities would inappropriately exclude designated impurities ——————————— ———. Please adopt the acceptable wording provided in your March 08, 2000 amendment and as further described in our December 12, 2000 letter to you [e.g., Total Impurities (except ——————————————— %].

Your response should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: CENTRAL DOCUMENT ROOM
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

When you amend your DMF ———, please notify the review chemist at the address below that the DMF has been amended. If feasible, please also provide the review chemist with a desk copy of your response in this case to facilitate its review.

Rik Lostritto
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, you may contact Anna Marie Homonnay, R.Ph., Regulatory Management Officer, at (301) 594-5535.

Sincerely,

/S/

Robert H. Seevers, Ph.D.
Chemistry Team Leader, Psychiatric Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

1. In reviewing the proprietary name ' , the primary concern was the possibility of confusion between the currently marketed extended-release tablet formulation of methylphenidate "Metadate ER", and the proposed '
There are two commonalties associated with these products. First, the products have the same proprietary name and secondly, each markets a 20 mg strength. There are two major differences between Metadate ER and are the different pharmacokinetics with regards to the rate of elimination and the dosing interval (TID and QD). 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.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confusion between and "ER" as anticipated, however there were several responses that did not include any modifier. Although the studies did not detect confusion between and "ER" at this time, OPDRA still believes the potential still exists given the modifiers are only one character letter off from each other. In a busy pharmacy setting with increased noise levels the two names could easily be misinterpreted on a verbal order.

2. The proposed established name (Methylphenidate Hydrochloride modified-release capsule) is not an approved pharmaceutical dosage form according to the United States Pharmacopeia (USP). OPDRA contacted Dan Boring, Chair of CDER Labeling and Nomenclature Committee, to discuss the recommended established name of this product. It was recommended the firm adopt "extended release" as the modifier. Therefore, the established name of the product should be Methylphenidate Hydrochloride Extended-release Capsules. Once the established name is revised the modifier which represents would be meaningless.

2. ' ' is also a common medical abbreviation for the following: maddox rod, magnetic resonance, manifest refraction, may repeat, measles-rubela, medical rectus, medical record, mental retardation, milliroentgen, mitral regurgitation, and moderate resistance. The use of the modifier may cause confusion in the hospital setting where ' ' might be interpreted as ' ' on an inpatient prescription order resulting in the administration of an additional dose of the medication.

For these reasons, we do not recommend use of the modifier

JUL 26 2000

Medeva Pharmaceuticals, Inc.
Attention: Norma J. Cappetti
Director Regulatory Affairs
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710

Dear Ms. Cappetti:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] (methylphenidate hydrochloride modified-release) Capsules .

We are reviewing the clinical section of your NDA and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

We note that a change of the randomization scheme was indicated, but no further documentation was provided. In this regard, we have the following requests:

1. Please provide all related documents with regard to which procedures were adopted to assure the blinding and treatment allocation balance during the switching of the randomization scheme from the [redacted] to the regular stratified randomization including the dates (e.g. IRB approval dates) and documentation of switching the randomization scheme for each (or all) site(s).

2. The sponsor's, or the CROs', SOP (whichever was followed) regarding to the randomization procedure should be provided.

3. Please provide any documentation of how the randomization was conducted for this trial, specifically with regards to the following: 1) who was in charge of the adaptive or stratified randomization when a new patient was ready for randomization 2) who had knowledge of the randomization scheme or was informed of the change of randomization scheme. In addition, please clarify how blocking was implemented in the randomization scheme.

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

Sincerely,

/S/

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

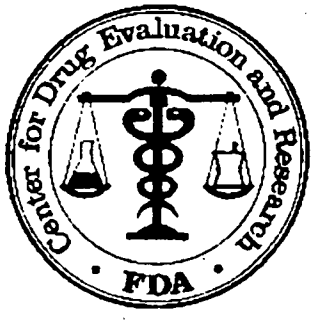
facsimile
TRANSMITTAL

[redacted]

To: Norma Cappetti
Sponsor: Medeva
Fax #: (716) 272-3952
Re: 21-259
Date: 5/25/00
Pages: (including cover sheet) 2

Please find attached our request for additional information which would facilitate our review of your application. If you should have any questions, please call.

Thanks



From the desk of...

Ms. Anna M. Homonnay-Weikel, R.Ph.
Project Manager
Division of Neuropharmacological Drug
Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857
301-594-5535
Fax: 301-594-2859

Additional requests resulting from the 45-day filing meeting:

Biopharmaceutics Issues:
Although you have provided study reports electronically, the data in these Word-documents are not easily convertable to Excel or ASCII-files; therefore, please provide the following data electronically, and if possible, as Excel files (or ASCII files):

Study MAI-1001-01 – demographics (age, weight, height), plasma concentration – time data, pharmacokinetic parameters (files corresponding to Tables 1-14 in the study report).

Study MAI-1001-02 – individual demographics (age, weight, height), individual plasma concentration – time data, individual pharmacokinetic parameters, individual effect (SKAMP deportment, attention; CLAMP Conners global index) – time data

Study MAI-1001-05 – demographics (age, weight, height), plasma concentration – time data, pharmacokinetic parameters (files corresponding to Tables 1.2-14 in the study report)

Study ———— demographics (age, weight, height), plasma concentration – time data, pharmacokinetic parameters

In vitro dissolution data used for the IVIVC (both individual and mean dissolution for all units used in the correlations)

The reviewer would also like to have *desk copies* of two studies located in NDA volumes 15 (non-clinical section 5), and a *desk copy* of a dissolution report:

1. Study 1193/63 (Methylphenidate: *In vitro* metabolism of the racemate and of the *d*- and *l*-enantiomers in human liver microsomes), Vol.15, p 5-2258
2. Study 1193/64 (Methylphenidate: *Effects of the* of the racemate and of the *d*- and *l*-enantiomers on selected cytochrome P450 activities in human liver microsomes), Vol.15, p 5-2258
3. Eurand America, Inc., Document number PF114-V2: 'The validation of assay, content uniformity, dissolution, and related substance methods for methylphenidate hydrochloride modified-release capsules, 20 mg.' Reference 3, in Pharmacokinetic Summary, Section 6.7, page 6-0185

CMC Requests:

Please provide the CMC section in electronic word documents as much as possible, especially the section concerning stability studies.

The following questions were raised at the meeting and should be addressed in the NDA:

Biopharmaceutical Issues:

For Study 01:

Clarify the population.
Clarify the strengths.
Was 90% confidence interval tested?

For Study 05:

Was drug given with food?

PK data is needed for approval of the strength, including single and multi-point PK profiling and maybe food effect.

Medeva

Medeva Development
1265 Drummers Lane, Suite 300
Wayne, PA 19087
Telephone: (610) 341-9280
Fax: (610) 341-9474

Regulatory Affairs

December 22, 1999

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120
Food and Drug Administration
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Woodmont Office Complex II
1451 Rockville Pike
Rockville, MD 20857

N(026)GC
ORIGINAL

IND 52,318 - Serial Number 026
Methylphenidate Hydrochloride Modified Release Capsules
General Correspondence: Minutes from Pre-NDA Meeting

Dear Dr. Katz:

Reference is made to the Pre-NDA meeting of December 9, 1999 and to the Medeva facsimile dated December 13, 1999 which provided our understanding of the discussions and agreements reached at the meeting.

Since data analysis of the pivotal trial is imminent, we are formally submitting the attached meeting minutes at this time and plan to proceed accordingly.

We appreciated the opportunity to meet with the Division.

If you have any questions regarding this submission, please contact the undersigned at 716-274-5826 or Monroe I. Klein, Ph.D., Executive Vice President, Regulatory Affairs at 610-341-9295.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Director, Regulatory Affairs

Desk Copy (Cover Letter): Anna Marie Homonnay-Weikel

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: December 31, 1999.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR	2. DATE OF SUBMISSION
Medeva Americas, Inc.	December 22, 1999
3. ADDRESS *(Number, Street, City, State and Zip Code)* 1265 Drummers Lane Suite 300 Wayne, PA 19087	4. TELEPHONE NUMBER *(Include Area Code)* (610) 341-9280
5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)* Methylphenidate	6. IND NUMBER *(if previously assigned)* ———

7. INDICATION(S) *(Covered by this submission)*
Attention Deficit Disorder

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _ ___ *(specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION.

[ ]

10. ***IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER: S-026

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S)
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☒ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35(b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35(a)** ☐ **CHARGE REQUEST NOTIFICATION 21 CFR 312.7(d)**

FOR FDA USE ONLY
CENTER FOR DRUG EVALUATION AND RESEARCH

CDR/DBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
	DEC 29 1999 RECEIVED HFD-120	DIVISION ASSIGNMENT:

002

CONTENTS OF APPLICATION

12

This application contains the following items: *(check all that apply)*

☒ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*

☐ 2. Table of contents *[21 CFR 312.23(a)(2)]*

☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*

☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*

☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*

☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
- ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
- ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572

☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
- ☐ Environmental assessment or claim for exclusion [21 CFR 312.23(a)(7)(iv)(e)]

☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*

☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*

☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED - *PLEASE NOTE THIS INFO WAS PREVIOUSLY SUBMITTED ON OCTOBER 5, 1999*

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

James Cappola, M.D., Ph.D.
Senior Vice President
Clinical Development, North America

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

James Cappola, M.D., Ph.D.
Senior Vice President
Clinical Development, North America

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Norma J. Cappetti Director, Regulatory Affairs	Norma J. Cappetti	
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
1265 Drummers Lane Suite 300 Wayne, PA 19087	(610) 341-9280	December 22, 1999

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

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Please DO NOT RETURN this application to this address.

FDA Contact Report

IND 52,318

Methylphenidate Modified Release Capsules

Minutes from FDA-Medeva Meeting December 9, 1999

FDA Attendees: Richard Chen, Biostatistical Reviewer; Roberta Glass, Medical Reviewer; Anna Marie Homonnay-Weikel, Project Manager; Kun Jin, Biostatistical Team Leader; Tom Laughren, Team Leader; Barry Rosloff, Pharmacology & Toxicology Reviewer; Vijay Tammara, Biopharmaceutics.

Medeva Attendees: Brian Dickson, Executive Vice President Clinical Development-Worldwide; Jim Cappola, Senior Vice President Clinical Research-US; Monroe I. Klein, Executive Vice President Regulatory Affairs-Worldwide; Wei, Du, Vice President Biostatistics and Dababase Management.

Introduction

Representatives from Medeva and from the Division of Neuropharmacological Products met in Rockville, Maryland on Friday, December 9, 1999 and held a Pre-NDA Meeting for Methylphenidate Modified Release Capsules.

Integrated Summary of Safety

Medeva's proposal for the Integrated Summary of Safety is acceptable to the Division.

Chemistry, Manufacturing, and Controls

A teleconference is scheduled for the week of December 12th to discuss chemistry, manufacturing, and controls issues. The meeting will include a recommendation from the biopharmaceutics group to develop a better dissolution method.

Biopharmaceutics

Medeva agreed to the following requests:

1. Clarify the patient population used in the biopharmaceutics studies
2. Include the 90% confidence intervals for study 01.
3. Provide steady state analysis of study 02.

4. Consider the labeling implications of administering the drug prior to breakfast in study 04.
5. Address the efficacy implications of the fact that the plasma levels for the modified release were lower than the sustained release in study 05.
6. Provide data from the biopharmaceutics studies in either ASCI or Excel format.

Biopharmaceutics advised that pharmacokinetic data (single and multiple dose studies evaluating the effect of food) is needed if the dosing and administration section of the labeling recommends dosing with It was agreed that this is a labeling issue for which there were two options:

1. Provide pharmacokinetic data to support the 60 mg dosing.
2. Recommend use of 20 mg and 40 mg dosing.

Clinical

The Division confirmed that they require case report forms for all serious adverse events as well as from deaths and dropouts due to adverse events. They also asked whether Medeva intended labeling for treatment of adult ADHD. Medeva responded that we are seeking class labeling for patients 6 years and older with ADHD, not a specific indication for adults. We agreed to provide a rationale for excluding one subtype of ADHD (inattentive) from our clinical studies (a common practice in clinical research with ADHD). Dr. Laughren suggested that the clinical pharmacology section might include a description of the population in study 04.

Statistics

Medeva agreed to FDA's request that there be a single primary efficacy endpoint. FDA requested we confirm that the primary score is the daily (combined AM and PM) score and that the analytical model compares differences from baseline using ANOVA and the last observation carried forward. Medeva also agreed to submit the SAS Proc Contents of Study 04 Dataset to FDA prior to the NDA submission.

NDA Submission

Medeva informed the Division that the target date for submission of the Methylphenidate Modified Release Capsule NDA is March/April 2000. Dr. Laughren indicated that this NDA could possibly go to an advisory committee meeting. Continuing, he explained that the class labeling for methylphenidate had not been revised in a long time and the Division might take this opportunity to use the advisory committee to address class labeling revisions.

IND 52,318

MAR 25 1999

Medeva Americas Inc.
Attention: Monroe Klein, Ph.D.
1265 Drummers Lane, Suite 300
Wayne, PA 19087

Dear Dr. Klein:

Reference is made to your Investigational New Drug Application (IND) for methylphenidate hydrochloride modified release capsules submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act.

Reference is also made to your February 18, 1999, protocol amendment (N-014) for changes to your potentially pivotal protocol, MAI 1001-04; and to your March 11, 1999, facsimile providing more detail regarding the use of an 'adaptive randomization system'.

Finally we refer to the March 15, 1999, teleconference between the FDA reviewing statistician, the FDA project manager and representatives of your company concerning statistical aspects of your protocol.

We have reviewed your revised protocol and have the following comments:

1. We do not find your proposal to conduct an 'adaptive randomization scheme' acceptable. In our view, you have not provided adequate justification for this methodology. Alternatively, we recommend that you utilize a conventional stratified randomization, which is accepted by the agency and which would be standard practice in this situation.

2. As discussed in the March 15, 1999, teleconference, the statistical plan should be more detailed and pre-specified. All important details of the proposed analysis should be clearly specified in the protocol. The vagueness and uncertainty of wording, such as expected and maybe, should be eliminated from the analysis plan. The primary efficacy variable should be clearly identified and defined. Your February 18, 1999, proposal, describing the primary and secondary analyses in the same paragraph in which you defined the primary efficacy variable, was confusing.

3. Please provide justification for your proposed method for handling missing data and specify how you plan to analyze the LOCF rank data. In addition, please note that we would like to see the traditional LOCF and observed cases (OC) analyses.

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

Sincerely yours,

/S/ 2/28/01

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 52,318

SEP - 4 1998

Medeva Americas Inc.
Attention: Monroe Klein, Ph.D.
1265 Drummers Lane, Suite 300
Wayne, PA 19087

Dear Dr. Klein:

Reference is made to your Investigational New Drug Application (IND) for methylphenidate hydrochloride modified release capsules submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act.

We have completed our review of your protocol entitled 'A Double-Blind Placebo Controlled Study of Modified Release (MR) Methylphenidate in Children with ADHD'(MAI 1001-04), and have the following comments:

1. There is some confusion about the inclusion/exclusion criteria for the different phases of the study, i.e., screening, placebo washout, and double-blind phases. Please clarify what the criteria are for each of these phases.

2. It is unclear why investigators are encouraged to drop subjects at visit 6 (at the end of Week 3 of the double-blind phase). While physicians should clearly act in the patient's best interests, they should be encouraged to keep patients in the trial except for important clinical reasons.

3. The protocol includes the following language: 'The statements which follow use the standardized effect size of 0.40 as estimated for the p.m., even though the actual means and standard deviation may not be properly identified.' Please clarify why it is not possible to obtain the actual means and standard deviation from previous studies.

4. The unit of efficacy measure is the average over the three observation days. Please be aware that the variances of these units will be different if for some patients one or two days (of measurements) would be missing. Please specify the statistical methods you will use to address this heteroscedasticity.

5. P-values for baseline and other covariate comparisons between treatment groups should be provided, although theoretically they may not be meaningful in some cases.

6. Overall, the statistical plan should be more detailed and more concretely pre-specified. The following are examples of where greater clarity is needed:

   -The circumstances under which the baseline score will be entered as a covariate should be specified for the statement, 'The baseline score, recorded at the end of the placebo washout week, may be entered as either a covariate or a differencing variable.'

   -Similarly, any vague wording in the protocol should be replaced with more definitive language, e.g., 'The primary analysis is expected to be a univariate analysis of covariance...', and, 'A non-parametric analysis of covariance may be used as supportive.'

   -Please indicate what the null hypothesis will be for the test done under the repeated measures analysis of variance. According to the protocol, 'If there is a significant treatment by time interaction, then the profiles will be checked for parallelism for the later time points in the study.' The algorithm or actions under each outcome of this check should be concretely pre-specified.

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

Sincerely yours,

/S/

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

Adequate animal studies for methylphenidate do not exist in several areas; the following would presumably be necessary for a new NDA:

1. Segment II reproduction in 2 species,
2. Segment III reproduction,
3. In vivo clastogenicity,
4. PK studies, primarily to determine the similarities or differences in metabolic pattern of methylphenidate across species (including humans) using relevant doses (i.e., doses used in the animal carcinogenicity and reproduction studies and human therapeutic doses). Comparison of metabolic pattern and degree of exposure would help in the evaluation of the relevance of animal findings to humans.

The following comments pertain to the Investigator Brochure:

1. P.10, first paragraph:
   Hepatoblastomas also seen in a low dose and medium dose male mouse.

2. P.10, second paragraph:
   The phrases " [redacted] ' and " [redacted] are speculative and should be removed.

3. P.11
   The table at the bottom should be removed [redacted], as should the last sentence ("[redacted]...").

Teleconference Record
Thursday February 8, 2001

Caller: Rik Lostritto

Called Norma Cappetti
Medeva America, Inc.
Rochester, NY 14603-1710

Time of call: 3:55 p.m. to 4:01 p.m.

Product name: Metadate methylphenidate controlled release capsules

Regarding: Document:Approvable letter dated 02/02/01

MINUTES OF THIS CALL

Medeva is correct; the proposed dissolution specification is ——— for the ER Beads at 2 hours; not ——— as appeared in the 02/02/01 AE letter.

However, given that the value at this dissolution testing time point for 3 batches is (batch EA-630), —— (EA-626) and —— (EA-623), this specification seems to be too wide and biased too low. The applicant was asked to consider a different specification for this time point (e.g., ——— in their response to the AE letter.

Rik Lostritto.

NDA FILING MEETING MINUTES

Date: May 24, 2000
NDA: 21-259
Location: Woodmont II, Conference Room E
Firm: Medeva Americas, Inc.
Drug: methylphenidate HCl Extended-release capsules
Indication: attention deficit disorder
Participants:

Russell Katz, MD
Thomas Laughren, MD
Roberta Glass, MD
Glenna Fitzgerald, PhD
Barry Rosloff, PhD
Maria Sunzel, PhD
Kun Jin, PhD
Kallapa Koti, PhD
Bob Seevers, PhD
Rick Lostritto, PhD

DISCUSSION:

Chemistry Issues:
Application is fileable. Sponsor should be requested to provide the CMC electronically in word format.

Biopharm Issues:
Application is fileable. Sponsor needs to provide the data electronically in Excel format.

Clinical Issues:
Application is fileable.

Statistical Issues:
Application is fileable; however, some aspects regarding the randomization methods will need clarification.

Preclinical Issues:
Application is fileable.

ADDENDUM:

A fax was forwarded to the sponsor on May 25, 2000, concerning the electronic data requirements. In addition, a letter concerning the randomization scheme was sent to the sponsor on July 26, 2000

/S/

Anna Marie Homonnay
Regulatory Project Manager

M E M O R A N D U M

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

DATE: March 23, 2001

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

SUBJECT: Recommendation for Approval Action for
Metadate CD (modified release methylphenidate) Capsules for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

TO: File NDA 21-259
[**Note:** This overview should be filed with the 2-13-01 response to our 2-2-01 approvable letter.]

In our 2-2-01 approvable letter, we proposed draft labeling, and we asked for (1) a regulatory status update, (2) the adoption of our proposed dissolution specifications, and (3) a commitment to conduct a phase 4 preclinical study on the effects of methylphenidate on developing systems. Finally, we conveyed several CMC questions and comments.

The sponsor responded with a 2-13-01 package that responded to all of these issues.

They have accepted our proposed dissolution specifications.

They have committed to conducting a preclinical study on the effects of methylphenidate on developing systems.

To my knowledge, they have adequately responded to all the CMC concerns.

We have had several exchanges and telcons with with sponsor regarding several remaining labeling differences, but we have now reached agreement on labeling as of 3-23-00.

I believe that Medeva has submitted sufficient data to support the conclusion that Metadate CD methylphenidate is effective and acceptably safe in the treatment of ADHD. I recommend that we issue the attached approval letter with our mutually agreed upon labeling.

cc:
Orig NDA 21-259
HFD-120
HFD-120/TLaughren/RKatz/RGlass/AHomonnay

DOC: MEMMETDT.AP1

MEMORANDUM

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

DATE: January 22, 2001

/S/

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

SUBJECT: Recommendation for Approvable Action for
Metadate CD (modified release methylphenidate) Capsules for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

TO: File NDA 21-259
[**Note:** This overview should be filed with the 3-31-00 original submission.]

1.0 BACKGROUND

Methylphenidate is a stimulant that has been available for many years in the US as a treatment for ADHD, both in an immediate release form (Ritalin) and in a sustained release form (Ritalin SR). Immediate release methylphenidate is rapidly cleared and needs to be given at least twice and often even three times a day. The necessity of giving methylphenidate at lunchtime in a typical school setting is considered a major disadvantage to the immediate release form. While Ritalin SR should theoretically preclude the need for multiple daily administrations, in practice this formulation has been viewed as less effective than immediate release methylphenidate given on a divided schedule. While it is not well understood why this is so, one view is that tolerance to the beneficial effects may occur as a result of a constant input.

On 8-1-00, Concerta, an OROS methylphenidate formulation was approved. Concerta was intended to partly mimic immediate release administration by providing an initial bolus in the morning (by dissolution of the drug overcoat), and then possibly exceed the benefits of a second immediate release dose at lunchtime by providing an increasing plasma methylphenidate concentration over the remainder of the day (by osmotic delivery of the core drug on the basis of an osmotic gradient). Presumably Concerta's major advantage is its effectiveness with only am dosing.

Like Concerta, Metadate CD is intended to partly mimic immediate release administration by providing an initial bolus in the morning (by dissolution of IR beads that comprise 30% of the dose), and then providing ongoing coverage over the rest of the day (by delayed and sustained dissolution of ER beads that comprise 70% of the dose). Again, Metadate CD's major advantage would presumably be its effectiveness with only am dosing.

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

IND 52,318 for the Metadate CD form of methylphenidate was originally submitted ——— Although we did not have an EOP2 meeting with the sponsor, we agreed in 6-25-98 correspondence to their plan to conduct a single adequate and well-controlled trial in children with ADHD in support of this new formulation. In a 10-9-98 amendment to this protocol (MAI 1001-04), the sponsor proposed an adaptive randomization procedure. In a 3-25-99 lettter we indicated that their justification for this change was not adequate, and we requested that they return to the originally planned stratified randomization, which they agreed to in a 5-13-99 amendment.

A preNDA meeting was held with the sponsor on 12-9-99.

The original NDA 21-259 for Metadate CD OROS methylphenidate was submitted 3-31-00, and was filed as a 505(b)(2) application. There were no safety updates to this application.

We decided not to take Metadate CD to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

The chemistry review was conducted by Richard Lostritto, Ph.D. As of this time, I am not aware of any chemistry issues that would preclude the approvability of Metadate CD. However, there was objection to the original name, We communicated this concern to Medeva, and they submitted two new names, i.e., Metadate CD or —— OPDRA, in an 11-10-00 e-mail expressed a preference for the Metadate CD name, and the sponsor has agreed to this name.

3.0 PHARMACOLOGY

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

4.0 BIOPHARMACEUTICS

The biopharmaceutics review was conducted by Maria Sunzel, Ph.D. As of this time, I am not aware of any biopharmaceutics issues that would preclude the approvability of Metadate CD. There had been a concern about the lack of PK data for the 60 mg dose, however, upon further consideration it was decided that it would not be necessary for additional PK information for this dose. The sponsor has shown dose linearity up to 60 mg (oral solution), and the relative bioavailability of the extended release capsule and oral solution is almost 100%.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Study Pertinent to Efficacy (MAI 1001-04)

The sponsor has provided data from one placebo-controlled clinical study in children with ADHD in support of the efficacy claim for Metadate CD, i.e., MAI 1001-04. The efficacy data were reviewed by Roberta Glass, M.D. of the clinical group and Kallappa Koti, Ph.D.of the biometrics group.

This was a randomized, double-blind, parallel group, 3-week, multicenter (32 US sites) study comparing Metadate CD and placebo in n=321 children aged 6-12 with ADHD (DSM-IV) who were either already considered responders to methylphenidate, or were methylphenidate naive but considered candidates for methylphenidate treatment. The sample included only patients who were of the combined type or the predominantly hyperactive-impulsive type; patients with the predominantly inattentive type were excluded. The methylphenidate dose was initiated at 20 mg qd, and could be increased at increments of 20 mg each week, based on clinical response and tolerability; thus, the maximum dose could be 60 mg qd in week 3. Dosing was before breakfast. The primary outcome was mean change from baseline of the averaged score (morning and afternoon) of the teacher's version of the Conners Global Index Scale at week 3 (i.e., an average of morning and afternoon scores for 3 days of each week). Secondary outcomes included mean change from baseline of: (1) the individual morning and afternoon scores of the teacher's version of the Conners Global Index Scale; (2) the parent version of the Conners Global Index Scale at week 3, completed on Saturday or Sunday, morning, afternoon, and evening; and (3) the CGI-I. For the primary outcome, ANOVA of the LOCF data was the protocol specified analysis.

It was my impression that the individual morning and afternoon scores of the teacher's version of the Conners Global Index Scale was considered by the sponsor to be the secondary outcomes of key interest, and although these were not explicitly identified as outcomes for conditional hypothesis testing in the protocol, I believe this was the intent, based on my notes of our meetings with the sponsor.

The mean age was about 9, and the sample was mostly male and Caucasian. 314 patients were available for the analysis in the ITT sample. Approximately 89% of the methylphenidate group completed to 3 weeks compared to 83% of placebo patients.

During week three, the predominant dose was 40 mg/day, however, there were substantial numbers at the 20 and 60 mg doses as well.

The mean changes from baseline for the teacher's version of the Conners Global Index Scale after 3 weeks of treatment were as follows:

Metadate CD
- AM —
- PM —

Placebo
- AM —
- PM —

The methylphenidate vs placebo comparisons were highly significant ($p<0.001$, LOCF) overall, and for both experienced and mph-naive patients. The comparisons were also highly significant ($p<0.001$, LOCF) for AM and PM separately. Although the afternoon scores were somewhat higher than the morning scores, the difference between drug and placebo were almost identical for both morning and afternoon, suggesting that the drug effect was the same for both times of day.

Drs. Glass and Koti concluded that this study supported the primary claim for overall efficacy of Metadate CD methylphenidate, and I agree.

5.1.3 Comment on Other Important Clinical Issues Regarding Metadate CD

Secondary Outcomes

On the secondary outcome of key interest, i.e., the individual morning and afternoon scores of the teacher's version of the Conners Global Index Scale, there was clear statistical significance at both times of the day. Thus, I am inclined to accept a mention of these findings in labeling. I discussed this issue with Drs. Jin, Koti, and Glass in a 12-20-00 meeting, and there was general agreement that the morning and afternoon findings could be noted in labeling.

Evidence Bearing on the Question of Dose/Response for Efficacy

Study 04 involved flexible dosing, and thus, there is no information in this study pertinent to dose/response for efficacy.

Clinical Predictors of Response

Dr. Koti conducted exploratory analyses for site, gender, race, and previous treatment, and found no differences in the primary outcome based on these subsets.

Size of Treatment Effect

While it is difficult to assign clinical significance to the observed differences between Metadate CD and placebo on the teacher's version of the Conners Global Index Scale, these differences are similar to those seen in other studies considered by most experts proof of efficacy of the IR product and were indistinguishable from the IR/placebo differences observed in these studies. Thus, I consider these clinically meaningful results.

Duration of Treatment

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

5.1.3 Conclusions Regarding Efficacy Data

In summary, I consider study 04 positive support for the claim of short-term effectiveness of Metadate CD methylphenidate in the treatment of ADHD. In the approval letter, we will need to ask Medeva to commit to conducting, postapproval, a study in children less than 6, under the Pediatric Rule.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for Metadate CD methylphenidate were reviewed by Dr.Roberta Glass (review dated 12-7-00). This original review was based on an integrated database including all subjects in the development program; apparently, all studies in the program were completed at the time of original submission of the NDA.

There were 2 studies in normal adults (PK), and 3 clinical studies in children with ADHD (ages ranging from 5 to 14). One of the ADHD studies was 04; the other 2 were open label, multiple dose titration studies. N=40 adults and n=188 children were exposed to Metadate CD in this program. The total person-years of exposure for children in the phase 2-3 ADHD program was about 10.5 patient years. Patients in phase 2-3 studies were roughly 80% male and predominantly white. The median age of patients was 9.

5.2.2 Adverse Event Profile for Concerta

5.2.2.1 Common Adverse Event Profile

The adverse event profile for Concerta was similar to that known for other methylphenidate products, including notably insomnia, anorexia, abdominal pain, and headache. Only 2 patients dropped out for adverse events: 1 for rash; another for headache, stomachache, and dizziness.

5.2.2.2 Conclusions Regarding Safety Data

Overall, there were no adverse event findings observed in the clinical trials with Metadate CD methylphenidate that would preclude an approvable action. The adverse event profile observed is similar to that seen with other methylphenidate formulations and it can be adequately characterized in labeling. Dr. Glass has suggested that we ask the sponsor to conduct a postapproval study to look at anorexia in association with the use of this product, since it must be given before breakfast. However, other methylphenidate products may also be given before breakfast, and often are. The recently approved Concerta labeling indicates that this product may be given before or after eating. The anorexia associated with methylphenidate is perhaps the most predictable of the adverse events associated with this drug, and is clearly labeled. Thus, it's not clear to me what the value would be in asking for additional study of this event.

5.3 Clinical Sections of Labeling

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

6.0 WORLD LITERATURE

There was no published literature to review that was specifically pertinent to the Metadate CD methylphenidate product.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Metadate CD methylphenidate is not approved anywhere at this time. We will ask for an update on the regulatory status of Metadate CD in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take Metadate CD methylphenidate to the PDAC.

9.0 DSI INSPECTIONS

Three sites were inspected for study 04, as follows:

While there were minor deviations, all data from the first two sites, and the data from all but 3 patients at the third site, were deemed acceptable in support of this NDA. DSI suggested excluding data from 3 patients at the third site for whom source materials were not available. We agreed that this exclusion would not have any impact on the overall outcome of this study.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft from the 3-31-00 original submission.

10.2 Approvable Letter

The approvable letter includes draft labeling and requests for a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

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

cc:
Orig NDA 21-259
HFD-120
HFD-120/TLaughren/RKatz/RGlass/AHomonnay

DOC: MEMMETDT.AE1

WITHHOLD 32 PAGE (S)

WITHHOLD 20 PAGE (S)

WITHHOLD 1 PAGE (S)

Facsimile Transmission

Medeva

Medeva Americas, Inc.
755 Jefferson Road
P.O. Box 1710
Rochester, NY 14603-1710
Telephone: (716) 274-5826
Fax: (716) 272-3952

Regulatory Affairs

Date:
October 17, 2000

To:
Ms. Anna Homonnay-Weikel
Project Manager

Company:
FDA, Division of
Neuropharmacological Drug
Products (HFD-120)

Fax No:
301-594-2859

From:
Norma J. Cappetti
Director, Regulatory Affairs

Pages (including cover):
4

Subject: NDA 21-259 methylphenidate hydrochloride modified-release capsules

Ms. Homonnay-Weikel,

Per our conversations last week and separate conversations I subsequently had with Ms. Sammy Beam in OPDRA per your recommendation we are requesting review of the attached two names which are different

We are also requesting that the established name methylphenidate hydrochloride modified-release capsules remain as is and have provided an explanation/justification for this in the attached letter.

Could you please provide a copy to OPDRA and to the Chemistry Team Leader Dr. Seevers and to other individuals that you deem appropriate.

Thank you for progressing this on an expedited bases.

Sincerely,

Norma J. Cappetti

Medeva

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Regulatory Affairs

BY FACSIMILE

October 17, 2000

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug
Products, HFD-120
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-259
Methylphenidate Hydrochloride Modified-Release Capsules
Amendment to a Pending Application: Proposed Brandname Suffix/Modifier and Continued Use of Modified-Release in Established Name

Dear Dr. Katz:

Reference is made to the pending new drug application identified above and to the October 11, 2000 facsimile received from the Division regarding the proprietary name, ' Capsules." Medeva was informed that " is not acceptable as a proprietary name, with the primary concern being the possibility of confusion between the currently marketed extended-release tablet formulation of methylphenidate, "Metadate ER." During a conversation between Ms. Sammy Beam and the undersigned on October 13, 2000, it was confirmed that the concern is with the modifier ' and that "Metadate" would be acceptable with a proper modifier to differentiate this product from the currently marketed extended-release product.

Medeva is hereby requesting consideration on an expedited basis per Ms. Beam of the following proposed proprietary names for this product:

1.) Metadate™–CD Capsules
(methylphenidate hydrochloride modified-release capsules)

2.) Metadate™- ——Capsules
(methylphenidate hydrochloride modified-release capsules)

Medeva intends for the proposed suffixes/modifiers "CD" (for controlled delivery of the modified-release formulation) and —— (for modified-release capsule), to identify this product as the modified-release formulation of Metadate and also serve to further differentiate this product from our currently marketed Metadate ER tablet product.

The facsimile of October 11, 2000 from the Division also stated that the proposed established name (methylphenidate hydrochloride modified-release capsule) is not an approved pharmaceutical dosage form according to the United States Pharmacopoeia (USP). The Division recommended that Medeva adopt "methylphenidate hydrochloride extended-release capsules."

The USP (Chapter 1090) discusses the following with respect to Oral Extended-Release Dosage Forms:

> "Modified-Release Dosage Forms – A modified-release dosage form is one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. Delayed-release and extended-release dosage forms are two types of modified-release dosage forms."
>
> "This document uses the term *extended release* to describe a formulation that does not release active drug substance immediately after oral dosing and that also allows a reduction in dosage frequency."

In addition, the following definition is provided in the FDA's Guidance for Industry, SUPAC-MR: Modified Release Solid Oral Dosage Forms (Sept. 1997):

> "Modified Release Dosage Forms: Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products."

Medeva believes strongly that it would be incorrect to identify this product as an extended-release product since it was specifically formulated to include both an immediate-release and an extended-release component as described below. We therefore re-request that the established name of this product remain as "methylphenidate hydrochloride modified-release capsules."

Methylphenidate hydrochloride modified-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose is provided by the IR component, and 70% of the dose is provided by the ER component. The plasma/time concentration profile shows two phases of drug release with a sharp, initial slope similar to methylphenidate immediate release tablet, and a second rising portion approximately three hours later, followed by a gradual decline similar to methylphenidate sustained-release tablet. Per the USP statement noted above, the term *extended release* describes a formulation that *does not* release active drug substance immediately after oral dosing.

Therefore, Medeva believes that it would not be accurate to refer to this product as "extended-release" as it is comprised of an immediate-release portion. In addition, it is necessary to differentiate this formulation from Medeva's currently marketed extended-release formulation that has the established name, "methylphenidate hydrochloride extended-release tablets, USP."

Medeva understands that the Division will pursue review of this name with the Office of Postmarketing Drug Risk Assessment and that acceptability of a suffix can be accomplished on an expedited basis. It is important to us that the modified-release terminology remain in the established name and for an appropriate, associated suffix be approved for use with this product as soon as possible.

If you have any questions, please contact the undersigned at (716) 274-5826, or Cheryl Rini at (716) 274-5346.

Sincerely,

Norma J. Cappetti

Norma J. Cappetti
Director Regulatory Affairs

cc: Ms. A.M. Homonnay-Weikel
Dr. R. Seevers