# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-284**

# MEDICAL REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

APPLICATION INFORMATION
NDA: 201-284
Sponsor: Novartis Pharmaceuticals Corporation
Date submitted: November 28, 2000
Date received: November 29, 2000
User fee due date: September 29, 2001

DRUG NAME
Drug: Methylphenidate HCl ——— release capsules (20, 30 and 40 mg)
Proposed Trade Name: Ritalin LA

DRUG CATEGORIZATION
Pharmacological Class: Psychostimulant
Proposed Indication: Attention Deficit Hyperactivity Disorder
Dosage Forms: 20, 30 and 40 mg modified release tablets
Route: Oral

REVIEWER INFORMATION
Medical officer: Andrew Mosholder, M.D.
Completion Date:

Contents

1.0 Material utilized in review

The original NDA submission comprised 45 volumes; case report forms were submitted on CD-ROM in PDF document format. The safety update was submitted 3/23/01.

2.0 Background

2.1 Indication

The following drug products are indicated for the treatment of attention deficit disorders, referred to as Attention Deficit/Hyperactivity Disorder (ADHD) in the DSM-IV.

Dexedrine (d-amphetamine sulfate) and Dexedrine Spansule sustained release capsules
Adderall (amphetamine and d-amphetamine, various salts)
Ritalin (methylphenidate HCl) and Ritalin SR sustained release tablets
Cylert (magnesium pemoline)
Desoxyn (methamphetamine HCl)
Concerta (methylphenidate HCl extended release tablets)
Metadate (methylphenidate HCl modified release tablets)

All are classified as psychostimulants, and are controlled substances in category II (except for Cylert, which is category IV). It will be seen from the above that there are modified release formulations approved for d-amphetamine and methylphenidate. Methylphenidate and amphetamine are older drugs, and were granted approval under the DESI process.

Sustained release Ritalin was approved without efficacy trials, and some have suggested that its efficacy is not as robust as immediate release Ritalin, perhaps due to insufficient Cmax values, or due to tachyphylaxis of the stimulant effect (see Swanson et al., Clin Pharmacol Ther 1999; 66:295-305).

This product is designed to provide a bimodal release of methylphenidate with a single daily dose, mimicking twice a day dosing with immediate release methylphenidate. The capsules can be opened and the contents sprinkled into food (see below).

2.2 Related IND

The IND for this drug product is [redacted]

2.3 Administrative History

[redacted] was opened with Protocol 02, a laboratory classroom single dose study (see below), submitted 8/17/98. At that time there had been one foreign bioavailability study completed in adults, Protocol 01.

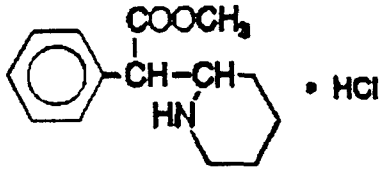
Representatives from Novartis and FDA held an "End of Phase II" meeting 5/5/99 to discuss the development program for this product. At that meeting, FDA advised Novartis to conduct an outpatient parallel group pivotal study, since Protocol 02 by itself would not support approval.

The pre-NDA meeting for this product was held on 4/4/00.

Note that the original name for this product was Ritalin — However, FDA's Office of Postmarketing Drug Risk Assessment found this name to be problematic, because of the potential for confusion with the traditional prescription directions QID and — . This concern was communicated in a letter to Novartis dated 9/30/99. In this clinical review, the product will be designated Ritalin LA.

2.4 Proposed directions for use

Ritalin LA is intended for once-a-day dosing in the morning. The proposed labeling indicates that it may be taken with or without food, and may be sprinkled over applesauce after opening the capsule. The total daily dosage of Ritalin LA should equal the daily amount of methylphenidate a patient takes with immediate release methylphenidate or Ritalin SR.




2.5 Financial disclosure

No principle investigator disclosed a financial interest that would have been affected by the results obtained. The only investigators who did not respond to Novartis' inquiry about financial conflict of interest were subinvestigators at . —— —— site.

3.0 Chemistry

The structural formula for methylphenidate is shown at left, from the sponsor's draft labeling. The chemical name is · —— . There are two asymmetric carbons in the structure of methylphenidate; the marketed compound is a racemic mixture of (+) and (-) threo enantiomers.

The Ritalin LA capsules contain equal portions of immediate release and delayed release beads. The immediate release beads consist of a coating of methylphenidate HCl over sugar spheres, and covered with —— The delayed release beads consist of immediate release beads to which an overcoat of —— r is applied. The . —— employed is a mixture of . —— —— both types appear in currently marketed drug products.

4.0 Preclinical data

As part of the development program for this product, Novartis undertook certain preclinical studies that are now routine, but had never been conducted for methylphenidate. These included new reproductive and developmental toxicity studies. Please refer to the pharmacology review for details.

5.0 Clinical data sources

The following table summarizes the clinical trials in this application. (Note: Ritalin —— 20 mg is the to-be-marketed formulation, referred to as Ritalin LA.)

Clinical pharmacology trials

| | |
|---|---|
| Protocol 01 | Bioavailability study comparing single doses of Ritalin LA 20 mg, Ritalin —— 20 mg and marketed Ritalin 10 mg BID; N=9 adult volunteers |
| Protocol 04 | Food effect study comparing bioavailability of Ritalin LA 40 mg administered fasting, with high fat meal and with applesauce. N=18 adult volunteers |
| Protocol 06 | Bioavailability study comparing single doses of Ritalin LA 40 mg versus marketed Ritalin 20 mg BID; N=17 adult volunteers |
| Protocol 09 | Four way crossover food effect study, comparing bioavailability of single doses of Ritalin LA 20 mg and Ritalin —— 20 mg, administered either fasting or with a high fat meal. N=15 adult volunteers. |

Clinical Trials–efficacy

| | |
|---|---|
| Protocol 02 | Two center (laboratory classroom), randomized, double blind, placebo controlled, single dose, 5 way crossover study. Ritalin —— 17.5 mg, Ritalin (Ritalin LA) 20 mg, Ritalin —— 25 mg, Ritalin —— 20 mg, and placebo; subjects received open label marketed Ritalin in between double blind laboratory classroom dosing days. N= 34 children aged 6-12 receiving methlyphenidate for ADHD prior to enrollment.. Pharmacokinetic blood samples were obtained in addition to efficacy measures. |
| Protocol 07 | Multicenter, randomized, double blind, placebo controlled, parallel group study. Phase 1: Subjects titrated to optimal dose of open label Ritalin LA over 4 weeks. Phase 2: One week single blind placebo washout. Phase 3: Double blind treatment with Ritalin LA (at best dose of 10, 20, 30 or 40 mg/d) or placebo for two weeks. N=161 children aged 6-12 with ADHD. A 12 week open label extension phase (protocol 07E) included 125 of these children (data submitted in safety update). |

Numbers of subjects exposed

According to the sponsor's Integrated Summary of Safety, a total of 256 subjects received one or more doses of the to-be-marketed Ritalin LA formulation. Of these, 61 were healthy adult volunteers in bioavailability studies, and 195 were children 6-12 years old with ADHD (34 of these were subjects in Protocol 02 and 161 were subjects in Protocol 07).

In Protocol 07E, the open label extension of Protocol 07, a total of 125 subjects received Ritalin LA; some of these subjects had received placebo in the double blind phase of Protocol 07, but of course all had received Ritalin LA in the open label run-in phase.

Of the 195 children who received Ritalin LA, 34 were enrolled in protocol 02 and received only single doses of the 4 formulations tested (one of which is the to-be-marketed formulation). Thus, there were 161 subjects who received multiple doses of Ritalin LA, all of them children with ADHD enrolled in Protocol 07. This group of subjects is considered the most relevant for determining the safety profile, and is

designated the key safety population in the sponsor's ISS.

Demographic characteristics

Healthy volunteers (n=61): These subjects were mostly white (71%), and male (75%), and had a mean age of 30 years.

Pediatric subjects: In Protocol 02, the 34 subjects who received a single dose of Ritalin LA were mostly male (77%) and white (77%) with a mean age of 10 years (range 7-12). In Protocol 07, of the 161 subjects, 73% were male, and 87% were white; the mean age of the subjects was 9 years (range 6-14), and 94 were naive to methylphenidate treatment.

Duration of exposure and dose

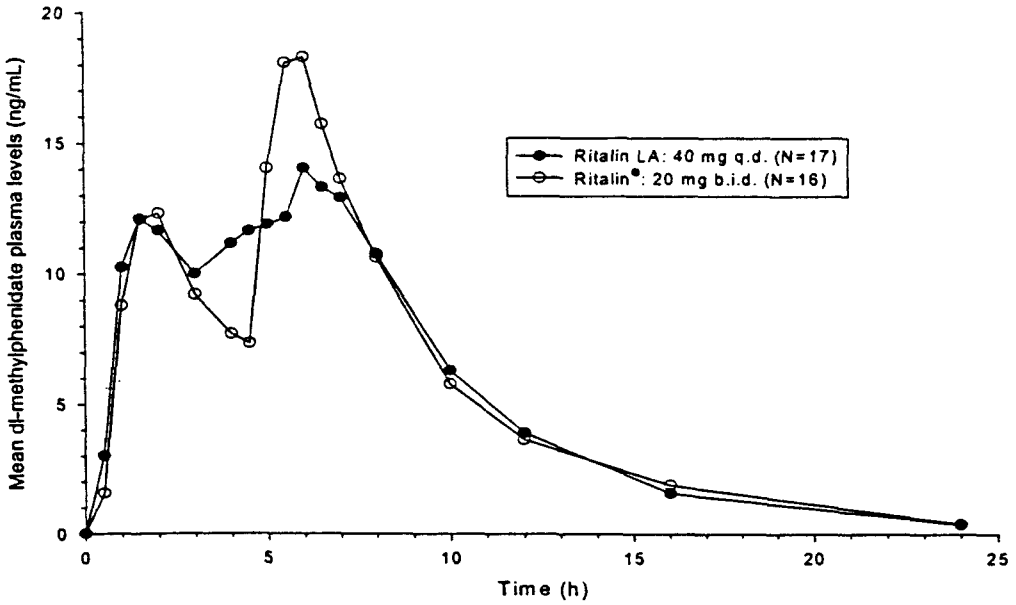
As noted, only protocol 07 involved multiple doses; in this study the mean duration of exposure was 35.7 days. In this trial subjects were titrated to their optimum dosage of Ritalin LA; the numbers of subjects receiving each daily dose in the double blind portion of the study is shown below.

| Best Dose | 10 mg | 20 mg | 30 mg | 40 mg | Total Ritalin LA | Placebo |
|---|---|---|---|---|---|---|
| N | 3 | 15 | 14 | 33 | 65 | 71 |

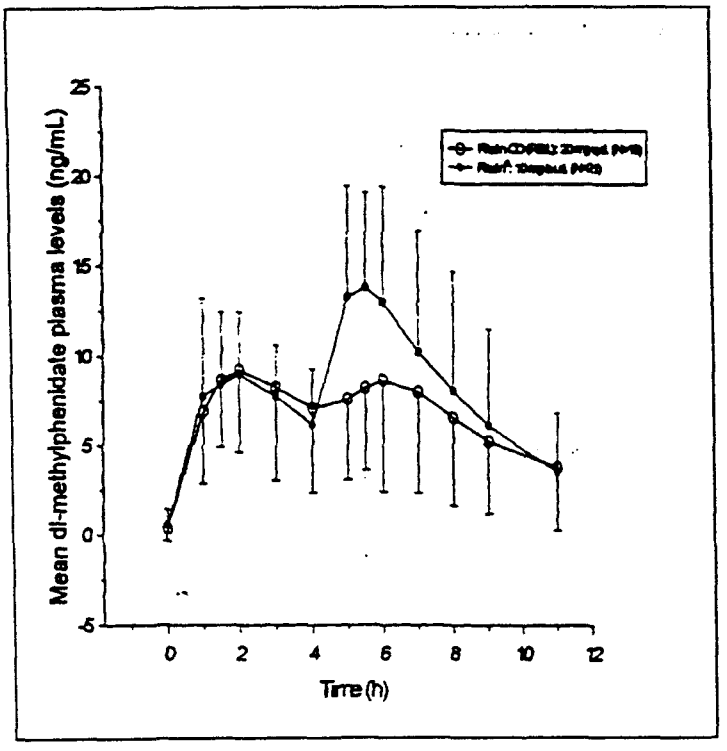
In addition, 125 subjects from study 07 received up to 90 days of open label treatment with Ritalin LA under protocol 07E.

6.0 Human Pharmacokinetics and Bioavailability

The following graph is taken from the sponsor's draft labeling and shows the plasma concentration-time curve from study 06, the bioavailability study in 17 healthy adults. The treatment conditions are Ritalin LA 40 mg and two doses of immediate release Ritalin 20 mg.



Below is the sponsor's figure showing the plasma concentration-time curve from Protocol 02, in which children were administered 20 mg of Ritalin LA and 10 mg BID of standard Ritalin.




The sponsor concluded from study 04 that food does not significantly alter the bioavailability for this drug product, but the review team from OCPB did not agree with this assessment. Please refer to the biopharmaceutics review by Dr. Ronald Kavanagh for details.

As discussed in Dr. Kavanagh's review, the initial release of methylphenidate is roughly comparable to that of immediate release Ritalin, while the second release is somewhat delayed, and the inter-peak trough concentration is lower with Ritalin LA than with marketed immediate release Ritalin given at morning and mid-day.

7.0 Efficicay

7.1 Overview of studies pertinent to efficacy

There are two studies intended to support the efficacy of this product, protocols 02 and 07. Please see the table in section 5.0 for a description of these trials. In protocol 02, subjects were observed in a laboratory classroom setting following single doses of Ritalin LA, and in protocol 07, subjects received two weeks of double blind treatment with Ritalin LA or placebo, and were assessed as outpatients in their communities.

7.2 Summary of individual studies pertinent to efficacy

7.2.1 Protocol 02

The orginial protocol was amended twice, and the description below incorporates the changes made to the protocol in these amendments.

Investigators/sites

Objective

According to the protocol, the primary objective of this study was to assess the pharmacodynamic profile of four different formulations of modified release Ritalin. The secondary objectives were to determine bioavailability and tolerability of the formulations.

Population

The protocol specified that the subjects were to be 40 boys or girls aged 6-12 years, with ADHD combined type (DSM-IV). Subjects were to be receiving methylphenidate 20 mg/day. Girls of child bearing potential were to be tested for pregnancy, and concomitant psychotropic medications were not allowed.

Design

This was a double blind, randomized, five period, single dose crossover study. Screening assessments included physical examination, clinical laboratories including pregnancy testing, and WISC-III; in addition, subjects and their parents or guardians visited the laboratory classroom for an orientation session.

The study itself consisted of a baseline period and 5 treatment periods. For the baseline phase, subjects were to receive open label marketed Ritalin 10 mg, in the morning and at midday, for six days. A third dose of Ritalin in the afternoon was permitted as needed, but not on the day before the laboratory classroom session. On the 7th day, subjects were to report to the laboratory classroom for a full day of baseline pharmacodynamic and pharmacokinetic assessments; on this day the subjects also were to receive marketed Ritalin 10 mg at 7:30 am and 11:30 am.

The procedures for the double blind crossover portion of the trial were similar. In between laboratory classroom sessions, subjects were to be treated with open label Ritalin 10 mg twice daily; the period in between laboratory classroom sessions was not to exceed 13 days. On each laboratory classroom day, subjects were to be administered a single dose of one of the following 5 treatments: Ritalin 17.5 mg, Ritalin 20 mg, Ritalin 25 mg, Ritalin 20 mg, or placebo. Concomitant medications were not permitted. All subjects were to receive each of the 5 double blind treatments in a crossover; thus the total number of laboratory classroom assessment sessions was six (including the baseline session).

Scheduled efficacy assessments included SKAMP ratings obtained for eight separate 20 minute periods throughout the day, and paper and pencil math tests administered eight times during the day.

Pharmacokinetic samples were scheduled at 13 timepoints during the 12 hour laboratory classroom day for a subgroup of 20 subjects; the other 20 subjects were scheduled for a more limited sampling (4 samples at 2, 4, 6, and 8 hours post dosing).

Analysis

The efficacy analysis as amended (Amendment #1) specified that the primary outcome comparisons would be between the two 20 mg formulations and placebo, adjusted for multiple comparisons to maintain an alpha level of 5%. The model specified was analysis of variance with subject, treatment, classroom, and period-nested-in-classroom as factors. The preselected primary variable was the area under the curve (AUC) of the SKAMP attention scores. The SKAMP deportment scores and math test scores, as well as AUC for the afternoon SKAMP scores only, were designated secondary measures.

Results

Patient flow

Forty-nine subjects were screened, and 40 entered the baseline study phase. Six subjects dropped out during the baseline phase (reasons: withdrawal of consent--5 subjects, and administrative problems--1 subject). Thus 34 subjects were randomized, and all 34 completed the protocol.

Subject characteristics

The following summarizes the characteristics of the 34 subjects who were randomized.

Mean age = 9.6 years
Age range = 7-12 years
Gender: 26 boys, 8 girls
Race: 26 White, 2 African-American, 1 Asian, 5 Other
Mean School grade = 4th

One subject had a tic disorder; otherwise there were no comorbid psychiatric diagnoses among the subjects. As stipulated by the protocol, all subjects had previously received methylphenidate.

Efficacy

The following displays the least square mean estimates of the SKAMP attention score AUC, by treatment. For this analysis the sponsor added a period-by-classroom interaction term to the model (not specified by the protocol). It should be noted that the [redacted] formulation is the formulation to be marketed.

| Treatment | N | Mean AUC-SKAMP attention | p-value versus placebo |
|---|---|---|---|
| 17.5 mg [redacted] formulation | 34 | 16.8 | <0.001 |
| 20 mg [redacted] formulation | 32 | 16.7 | <0.001* |
| 20 mg [redacted] formulation | 34 | 16.7 | <0.001* |
| 25 mg [redacted] formulation | 33 | 15.7 | <0.001 |
| Placebo | 32 | 19.8 | - |

*corrected for multiplicity

Thus both the 20 mg formulations tested were superior to placebo on the primary outcome measure, as were the 17.5 mg and 25 mg dosages. In addition, statistical superiority was demonstrated for all 4 active treatments on the secondary outcome measures: AUC for SKAMP-attention in the afternoon only, AUC for SKAMP-deportment (both whole day and afternoon alone scores), and the math test scores.

From the pharmacokinetic results, the sponsor concluded that the 20 mg [redacted] Formulation demonstrated bioavailability that most closely resembled Ritalin 10 mg BID. Accordingly, it was selected for development as the to-be-marketed formulation.

Conclusions

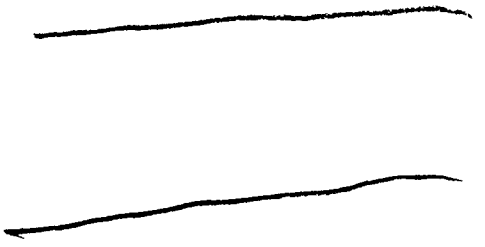
This study provides evidence that the drug product is effective in the treatment of ADHD. However, the design of the study (i.e., a single dose crossover trial in a highly structured laboratory classroom setting) limits the generalizability of the results somewhat.

7.2.2 Protocol 07

Investigators/sites

Novartis awarded a contract to [redacted] to conduct this study.
The following investigators were listed in the study report:

[redacted]



However, although this list includes 14 U.S. sites, the study report states there were 13 U.S. sites and 2 Canadian sites; the status of the 14th U.S. site was unclear.

Objective: The purpose of this study, as stated in the protocol, was to assess the safety and efficacy of Ritalin LA versus placebo in children with ADHD.

Population: Children aged 6-12 years with ADHD (any type) were eligible, regardless of whether they were previously treated with stimulants or not. A structured diagnositic interview, the Diagnostic Interview Schedule for Children (DISC-4.0), was to be used to confirm the diagnosis. The protocol specified a sample size of 128 subjects. Among the exclusion criteria were concomitant psychotropic medication use, substance abuse by the subject or a family member, and pregnancy.

Design: Up to 6 weeks were allowed to complete the screening assessments. These were to include history and physical examination, DISC-4.0, pregnancy testing, clinical laboratories, and drug screening. Next, eligible patients were to receive single blind Ritalin LA treatment, titrated to the best dose of either 10, 20, 30 or 40 mg daily over a 4 week period. When considered stable for two weeks, subjects were to receive one week of single blind placebo treatment. At the end of this placebo washout, baseline assessments were to be obtained and the subject was to be randomized to either their previous optimal dose of Ritalin LA or to placebo. The duration of this double blind phase was to be 2 weeks, and it was to be followed by an optional 12 weeks of open label Ritalin LA treatment. Safety assessments included vital signs, weight, height, clinical laboratories, and adverse event monitoring. Efficacy assessments included CGI scores and Conners ADHD DSM-IV Scales (CADS) completed by teachers and parents. The original protocol was never amended.

Analysis: The protocol states, "The main analysis will be an analysis of covariance on the change from baseline to the final rating in the DSM-IV total subscale score of the CADS-T. Treatment group, center, and the baseline score of the DSM-IV total subscale will be used as exploratory variables in the model." The baseline assessment was defined as the assessment at the end of the single blind placebo week, and the intent-to-treat population was defined as all patients administered double blind treatment with one or more post-randomization CADS-T evaluations.

Results

Patient flow: One hundred and sixty four subjects entered the open label titration phase of the study, and of these, 26 discontinued prior to the single blind placebo phase. The reasons for discontinuation from the open label titration were as follows:

| Reason | number of subjects |
|---|---|
| Lack of effect | 7 |
| Withdrawal of consent | 6 |
| Adverse event | 4 |
| Administrative problem | 4 |
| Lost to follow up | 3 |
| Protocol violation | 2 |
| Any reason (total) | 26 |

During the single blind placebo week one subject withdrew consent to participate, leaving 137 subjects to enter the randomized treatment phase. The table below summarizes the disposition for the 2-week randomized treatment period of the study. The majority of subjects in both treatment groups completed the entire two week period of double blind medication treatment.

| Double-blind treatment | Ritalin LA | Placebo |
|---|---|---|
| Randomized (n) | 66 | 71 |
| Discontinued for adverse events (n) | 2 | 1 |
| Discontinued for lack of effect (n) | 1 | 1 |
| Withdrew consent (n) | 1 | 0 |
| Discontinued for administrative problem (n) | 1 | 0 |
| Intent-to-treat (n) | 63 | 71 |
| Completed (n) | 61 | 69 |

Subject characteristics: The baseline and demographic characteristics of the 136 subjects who were randomized were comparable to those of the 164 subjects who entered the open label titration period (table 7-4 in the clnical study report, data not reproduced here). The following table shows the demographic characteristics of the subjects randomized:

| Double-blind treatment | Ritalin LA | Placebo |
|---|---|---|
| Randomized (n) | 65 | 71 |
| Gender (%male:%female) | 80:20 | 73:27 |
| Age, median (yrs) | 9 | 9 |
| Age, range (yrs) | 6-14 | 6-13 |
| DSM-IV type (n)<br>Inattentive<br>Hyperactive-impulsive<br>Combined<br>No DISC diagnosis | <br>18<br>2<br>42<br>3 | <br>8<br>0<br>60<br>3 |
| Baseline mean CADS-T total score* | 27.2 | 28.3 |
| Prior methylphenidate treatment (%)** | 46.2% | 42.3% |

*two subjects had no baseline scores

**reported as either methylphenidate or methylphenidate HCl

The most noticeable imbalance between groups was the prevalence of the inattentive subtype of ADHD, which was higher in the drug group (n=18) compared to the placebo group (n=8).

With respect to medical history, 13 of the 136 subjects randomized had a history of traumatic injury; accidental injury is thought to be associated with ADHD, perhaps because of impulsivity and hyperactivity. Thirty-four subjects had "personality disorder of childhood" and 20 had asthma. Adenoidectomy was the most common past surgical procedure (in 12 subjects). The drug and placebo groups were not very different regarding the prevalence of these comorbid conditions.

Dosing: The study report does not appear to contain a summary of the daily doses administered.

Concomitant medications: Acetaminophen and ibuprofen were the most commonly used concomitant medications during the trial.

Efficacy

Primary outcome measure: The table below displays the mean change from baseline to final observation on the CADS-T total subscale score.

| Treatment group | Ritalin LA | Placebo |
|---|---|---|
| N | 62 | 70 |
| Mean improvement from baseline | 10.7 | 2.8 |
| Standard Deviation | 15.7 | 10.6 |

The p-value from ANCOVA for the difference between treatment groups was < 0.0001. Note that 2 subjects had no baseline CADST scores, one from each treatment group. The sponsor included these subjects in the analysis of covariance by assuming that their change from baseline was zero.

Because the standard deviations for the drug and placebo groups differed by a substantial amount, the Biometrics reviewer, Dr. Kallappa Koti, confirmed the ANCOVA finding of statistical significance with a non-parametric test (Wilcoxon rank-sum test). Please refer to Dr. Koti's review for details.

Secondary outcome measures: the CADS-T inattentive and hyperactive-impulsive subscale results also robustly favored drug over placebo. Results on the parent version of the CADS also favored drug over placebo. A subgroup analysis according to ADHD type (n=100 combined type, n=26 inattentive type) showed statistical superiority for drug versus placebo in both diagnostic groups.

Conclusions

This study provides evidence that Ritalin LA is an effective treatment for ADHD. The enrichment design limits the generalizability of the results to some degree, in that all subjects randomized had already responded Ritalin LA in the first phase of the trial. In other words, the study showed that Ritalin LA was more effective than placebo for patients who had responded previously to open label Ritalin LA.

8.0 Safety

8.1 Safety methods

The original NDA submission included reports from pediatric clinical efficacy trials 02 and 07 and from adult clinical pharmacology trials 01, 04, 06 and 09. The NDA safety update provided the report from the 3-month open-label extension protocol for study 07, designated study 07E. This extension study has been completed and the safety update contains a full report of the clinical data. There are no ongoing clinical trials, and thus no outstanding safety data.

8.2 Deaths: None

8.3 Assessment of dropouts

8.3.1 Overall pattern of dropouts

The following table displays the number of patients by reason for premature discontinuation from the double blind phase of Protocol 07. However, it is important to remember that subjects entering double blind treatment had already received up to 4 weeks of open label Ritalin LA.

| Category | Ritalin LA (n) | Placebo (n) |
|---|---|---|
| Randomized | 66 | 71 |
| Completed | 61 | 69 |
| Discontinued for adverse events | 2 | 1 |
| Discontinued for lack of effect | 1 | 1 |
| Discontinued for other reasons | 2 | 0 |

8.3.2 Adverse events associated with dropouts

Phase I studies with healthy adult volunteers--There were 3 subjects who dropped out for adverse events: one for headache, nausea and hot flushes; one for an apparent panic attack; and one for nausea, vomiting and dizziness.

Studies with pediatric patients--There were no dropouts for adverse events in Protocol 02 or Protocol 07E. The following subjects dropped out for adverse events during open label run in treatment with Ritalin LA in protocol 07:

| Subject | Adverse event |
|---|---|
| 503/8 | Fatigue |
| 501/12 | Lethargy |
| 503/4 | Anger, hypomania |
| 506/9 | Anger |
| 513/6 | Anxiety and depressed mood |
| 501/7 | Migraine |

In addition, there was one adverse dropout during the double blind treatment phase of Protocol 07:

503/6 Depression (see below under Serious Adverse Events)

8.4 Serious Adverse Events: There were two such events.

Hospitalization for depression-- Subject 503/6, Protocol 07, Ritalin LA 30 mg/day (8 y.o. male)
Hospitalization for abdominal pain, which resolved without intervention-- Subject 512/3, Protocol 07E, Ritalin LA 30 mg/day (11 y.o. female)

8.5 Other safety findings

8.5.1 Adverse event incidence:

In the inital open label titration period for study 07 (n=161), the following adverse events were reported at an incidence of $\geq$ 5%:

| | |
|---|---|
| Headache | 11.8% |
| Insomnia | 9.3% |
| Upper abdominal pain | 6.8% |
| Appetite decreased | 6.8% |
| Anorexia | 5.6% |

In the subsequent 2-week double blind treatment phase, there were only 2 adverse events with an incidence > 2% in the drug group:

| Adverse event | Ritalin LA (n(%)) | Placebo |
|---|---|---|
| Anorexia | 2 (3.1%) | 0 |
| Insomnia | 2 (3.1%) | 0 |

In the open label extension under Protocol 07E, the most frequently reported adverse events (>2%

incidence) were insomnia (5.6%), headache (4.8%) and decreased appetite (3.2%).

8.5.2 Laboratory findings

The sponsor designated criteria for clinically notable abnormal laboratory values. In Protocol 02, a total of 8 such abnormalities included increased monocytes, increased eosinophils, increased WBC, and decreased neutrophils. The crossover design of the study makes interpretation of such findings difficult.

In Protocol 07, two Ritalin LA treated subjects had increased alkaline phosphatase, and two had decreased alkaline phosphatase; also, one Ritalin LA subject had an elevated WBC and one had a decreased lymphocyte count. One placebo patient had a high WBC.

With respect to changes in mean values for laboratory parameters, by inspection, the most notable difference observed in Protocol 07 between Ritalin LA and placebo was decreased mean alkaline phosphatase (-0.9 versus +5.4 U/L for Ritalin LA and placebo, respectively). This is statistically significant by a paired t-test (p-value $< 0.001$). However, Novartis did not provide any statistical analysis of changes in mean laboratory values.

There were no clinical laboratories obtained during Protocol 07E.

8.5.3 Vital signs, height and weight

Novartis defined criteria for clinically notable changes in vital signs. In Protocol 07, increased pulse rate was observed in 1.2 % of Ritalin LA patients and 1.4% of placebo patients, and decreased pulse rate was observed in 12.4% of Ritalin LA patients and 7.0% of placebo patients. For blood pressure, elevated diasystolic blood pressure was observed in 3.7% of Ritalin LA patients and 1.4% of placebo patients, and both high and low systolic blood pressure occurred in 1.9% of Ritalin LA patients and zero placebo patients.

The sponsor did not provide a statistical analysis of changes in vital signs, but by inspection there did not appear to be substantial differences in mean vital sign parameters between the Ritalin LA and placebo groups in Protocol 07. With respect to weight, in Protocol 07 for all treated patients (including those who received only open label Ritalin LA), the mean change in weight from baseline to endpoint was +0.1 kg for Ritalin LA and +1.0 kg for placebo. A two sample t-test (by this reviewer) showed this difference to be highly statistically significant.

Note that in Protocol 02, vital signs were not obtained during the laboratory classroom session, merely at baseline and the end of study visit.

In Protocol 07E, vital signs, height and weight were obtained at the final visit, but Novartis did not analyze these data.

8.5.4 Electrocardiograms: There were no electrocardiograms obtained in these clinical trials.

8.5.5 Overdosage: There were no Ritalin LA overdosages during clinical trials. Novartis points out in their proposed labeling that a physician treating an overdose of Ritalin LA should be aware of the possibility for delayed release of the drug substance.

8.6 Adequacy of safety assessments

The sponsor should perform statistical analyses on the vital sign data from Protocol 07, and should provide at least descriptive statistics for the vital sign, height and weight data in Protocol 07E. In other respects, the safety assessment was adequate for a new formulation of a marketed drug.

8.7 Overall conclusions about safety

Generally speaking the safety profile resembled that expected for methlyphenidate. The safety database was limited somewhat by the fact that there were no comparative data on treatment naïve subjects; i.e., all subjects in the placebo controlled phase of Protocol 07 had already been exposed to methylphenidate during the run-in period, if not before.

The finding of a net difference of 0.9 kg in mean weight between Ritalin LA and placebo subjects in Protocol 07 is concerning. The sponsor should be asked for a more detailed analysis; i.e., a presentation of the weight data by week of the trial, and by age and gender subgroups, along with hypothesis testing for the difference between groups. In addition, the sponsor should provide descriptive statistics for vital signs, height and weight in Protocol 07E.

9.0 Conclusions: In my view, the application is approvable from a clinical standpoint.

10.0 Recommendations

Novartis has proposed labeling that is generally acceptable. My suggested changes will appear in a separate document.

As noted above, the sponsor should be asked for a more detailed analysis of the weight data from Protocol 07; i.e., a presentation of mean weight by week of the trial, and by age and gender subgroups, along with hypothesis testing for the difference between treatment groups. In addition, the sponsor should provide descriptive statistics for vital signs, height and weight in Protocol 07E.

Andrew Mosholder, M.D.
Medical Officer, HFD-120

Cc: Laughren, Homonnay, Mosholder

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

/s/
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Andy Mosholder
9/12/01 05:19:54 PM
MEDICAL OFFICER

Thomas' Laughren
9/17/01 09:11:59 AM
MEDICAL OFFICER
Because of remaining serious CMC deficiencies, I am recommending a non approval action at this time; see memo to file for more detailed comments.--TPL

MEMORANDUM

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

DATE: September 17, 2001

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

SUBJECT: Recommendation for Non-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 11-28-00 original submission.]

## 1.0 BACKGROUND

Methylphenidate is a stimulant that has been available for many years in the US as a treatment for ADHD. It is available in an immediate release form (Ritalin and various generic versions of the IR), in several sustained release forms (Ritalin SR and various generic versions of the SR), and more recently in modified release forms, i.e., Concerta; and Metadate CD. The sustained release and modified release forms can be given qd. 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.

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.

Ritalin LA is a modified release formulation that, like Concerta and Metadate CD, can be given qd and is intended to essentially mimic the plasma levels seen when the IR is given in the morning and at lunchtime. Presumably Ritalin LA's major advantage is its effectiveness with only am dosing.
The recommended dose range for Ritalin LA is 20 to 40 mg/day. It will be available in capsules of 20, 30, and 40 mg strengths.

——— for this modified release methylphenidate was originally submitted 8-17-98.

An EOP2 meeting with the sponsor was held on 5-5-99, at which time we emphasized the need for a clinical study in a typical clinical setting. They had planned on conducting a laboratory classroom study as their only clinical study.

A preNDA meeting was held with the sponsor on 4-4-00. We discussed and provided advice on the two key studies (02 and 07). We indicated that, by design, study 07 should be an adequate study. However, we cautioned that study 02 was problematic because of its very complicated design, failure to identify primary outcomes, and multiplicity.

The original NDA 21-284 for Ritalin LA was submitted 11-28-00, and was filed as a 505(b)(2) application on 1-18-01. A safety update was submitted on 3-23-01 and was included in the clinical review.

We decided not to take Ritalin LA to the Psychopharmacological Drugs Advisory Committee.

## 2.0 CHEMISTRY

The chemistry review was conducted by Gupreet Gil-Sangha, Ph.D. The chemistry group is recommending a non-approvable action, based on the fact that Compliance has deemed the manufacturing site to be an unacceptable source of drug product due to a concern about possible data falsification. This judgement will stand until the site is re-inspected and cleared of such charges, however, as of the time of preparation of this memo, the site has stated that it is not ready for re-inspection. Thus, there remains a serious concern about the acceptability of the designated site as a source of drug product, and this concern is a sufficient basis, in my view, to conclude that this application is not approvable at this time.

There remain other minor deficiencies that can be conveyed in the nonapproval letter.

We are still waiting for OPDRA to make a recommendation on the proposed name, i.e., Ritalin LA.

## 3.0 PHARMACOLOGY

The original pharmacology/toxicology review was conducted by Ed Fisher, Ph.D. As of this time, I am not aware of any pharmacology/toxicology issues that would preclude the approvability of Ritalin LA. If and

when this application can be deemed approvable, the letter will need to communicate the necessity of a commitment to conduct juvenile animal studies post-approval.

## 4.0 BIOPHARMACEUTICS

The biopharmaceutics review was conducted by Ronald Kavanagh, Ph.D. Each Ritalin LA capsule contains a 50:50 mixture of immediate release (IR) and enteric-coated delayed release (EC-DR) beads. This product demonstrates a bimodal release pattern. The IR beads yield an initial peak at about 2 hours, and the EC-DR beads yield a second peak on average at 6.5 hours. The variability of when the second peak occurs is much greater for Ritalin LA given qd compared to Ritalin IR given bid, with a range of [redacted] hours. The second peak for Ritalin LA, although higher than the first peak, is lower than the second peak for Ritalin IR given bid. The interpeak minimum concentration for Ritalin LA is also higher than that seen with Ritalin IR given bid. Some patients given Ritalin LA have a second peak that may actually occur in the late afternoon or even early evening. Thus, Ritalin LA does not mimic the time concentration profile of Ritalin IR given bid as well as other recently approved methylphenidate controlled delivery products, i.e., Concerta and Metadate CD.

There is a clear food effect with a high fat breakfast, with a delay in lag time and a delay in time to first peak. The possibility of a food effect on the second peak has not been explored, however, it should be noted that study 07, the study supporting the approval of this product, was done without regard to timing or type of noon meal. Release of drug from the EC-DR beads is completely dependent on pH, however, the effect of concomitant use of antacids has also not been explored.
As of this time, I am not aware of any biopharmaceutics issues that would preclude the approvability of Ritalin LA. If and when this application can be deemed approvable, the letter might ask for a commitment to at least consider studies to explore food effect on the second peak and also the effect of concomitant use of antacids on the second peak.

## 5.0 CLINICAL DATA

### 5.1 Efficacy Data

The sponsor has provided efficacy data from two placebo-controlled clinical studies in children aged 6 to 12 with ADHD in support of the efficacy claim for Ritalin LA, i.e., 02 and 07. The efficacy data were reviewed by Andrew Mosholder, M.D. of the clinical group and Kallappa Koti, Ph.D., of the biometrics group.

#### 5.1.1 Summary of Studies Pertinent to Efficacy

##### 5.1.1.1 Study 02

This was a randomized, double-blind, 5-arm crossover study conducted in a laboratory classroom setting, at 2 different sites. Each treatment arm was 1 week, and the arms included 3 fixed doses of formulation 1 (17.5, 20, 25 mg), 1 dose of formulation 2 (20 mg), and placebo (all given in the morning). It should be noted that patients received experimental treatment only on the days in the laboratory classroom, and all received methylphenidate IR 10 mg bid on the other 6 days of each week. The population studied was children aged 6-12 with ADHD (DSM-IV) who were to already be taking methyphenidate 20 mg qd. It was not clear what method of randomization was used. Assessments were done in the laboratory classroom each Saturday, and included the following: SKAMP, Math tests, and PK at 0, 1.5, 3.0, 4.5, 6.0, 7.5, and 9.0 hours post dose. The primary outcome was AUC (0-9 hours post dose) for the SKAMP-Attention subscale. The protocol specified analysis was ANOVA.

A total of n=34 patients were randomized, and all were able to complete the 5 periods. The mean age was 10 years, and these were mostly males (77%) and the mostly white.

The sponsor's analysis of SKAMP-Attention subscales was highly significant in favor of all 4 MPH arms vs placebo. Secondary analyses, including separate morning and afternoon assessments of various measures were also significant in favor of the 4 MPH arms. However, Dr. Koti had many concerns about the study design and analysis plan. A primary concern was a failure to adequately justify the primary analytical method used. There were also discrepancies between the protocol, including the statistical analysis plan, and the study report.

Consequently, he has recommended against presenting any results pertinent to time course in labeling, the findings from this trial of greatest interest to the sponsor. The sponsor had hoped to indicate in the Clinical Trials section that study 02 demonstrated "[redacted] and "[redacted]

Comment: I agree that there are many questions that remain to be answered about the results from study 02 before we should consider adding information from this trial to labeling. Fortunately, the results of this trial are not critical to an approvable action, since study 07 is, by itself, sufficient to support the efficacy of Ritalin LA.

### 5.1.1.2 Study 07

This was a randomized, double-blind, parallel group, multicenter (13 US sites and 2 Canadian sites) study comparing Ritalin LA (10 to 40 mg/day; qAM schedule) and placebo in children aged 6-12 with ADHD (DSM-IV) who were either already considered responders to methylphenidate (about 45%), or were methylphenidate naive but considered candidates for methylphenidate treatment (about 55%). The sample included patients who were of the combined type, the predominantly hyperactive-impulsive type, or the predominantly inattentive type. The 2-week, double-blind phase was preceded by a pre-randomization phase including 3 periods: (1) a screening phase of up to 6 weeks; (2) a single-blind titration phase of 2-4 weeks; and (3) a 1 week single-blind placebo washout phase. The purpose of the titration phase was to

establish the optimal dose for each patient. During the 2-week randomized phase, patients were assigned either to continue on Ritalin LA (at their optimal dose) or to placebo.

The primary outcome was mean change from baseline (end of placebo washout) to endpoint (end of the 2-week double-blind period) on the Conners ADHD/DSM-IV Scale for Teachers (CADS-T). This scale maps exactly to the 18 items comprising the DSM-IV criteria (rated 0 to 3). The ratings were done weekly, based on the child's behavior in school over the previous week. The CGI was a secondary outcome. For the primary outcome, ANCOVA of the LOCF data was the protocol specified analysis.

The mean age was about 9, and the sample was mostly male and Caucasian. N=134 patients were available for the analysis in the ITT sample. Overall, 97% of the patients completed to 2 weeks. It was not clear what the distribution of Ritalin LA doses was in the double-blind phase, and we will need to request this information.

The mean changes from baseline for the CADS-T (i.e., baseline - final visit, so that a positive value indicates improvement) after 2 weeks of treatment were as follows:

| | | |
|---|---|---|
| Ritalin LA | +10.7 | |
| Placebo | - 2.8 | p< 0.0001 |

All of the secondary outcomes also significantly favored Ritalin LA over placebo.

Comment: Drs. Mosholder and Koti concluded that this study supported the primary claim for overall efficacy of Ritalin LA, and I agree.

### 5.1.2 Comment on Other Important Clinical Issues Regarding Ritalin LA

Secondary Outcomes

The secondary outcomes in study 07 were also positive, however, none of these were prespecified as key secondary outcomes, and none adds any critical information, in my view. Thus, we have not added any of these to labeling as proposed by the sponsor.

Evidence Bearing on the Question of Dose/Response for Efficacy

Neither study involved multiple fixed doses, and thus, there is no information in these studies pertinent to dose/response for efficacy.

Clinical Predictors of Response

There were insufficient non-Caucasian patients to conduct an analysis by race, and insufficient female patients patients to conduct an analysis by gender.

Size of Treatment Effect

While it is difficult to assign clinical significance to the observed differences between Ritalin LA and placebo on the CADS-T, these differences are similar to those seen in other studies considered by most experts proof of efficacy of the IR product. 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 Ritalin LA in ADHD.

### 5.1.3 Conclusions Regarding Efficacy Data

In summary, I consider studies 07 positive support for the claim of short-term effectiveness of Ritalin LA in the treatment of ADHD. If and when this application reaches an approval status, we will need to ask Novartis 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 Ritalin LA were reviewed by Dr. Andrew Mosholder. This original review was based on an integrated database including all subjects in the development program, and included information provided in a 3-23-01 safety update. All clinical trials with Ritalin LA were completed as of the time of the safety update, and all safety data were reported at that time. Thus, there is no need for an additional safety update.

There were 2 clinical studies in children ADHD (ages ranging from 6 to 12), i.e., studies 02 and 07. The remaining 4 studies were focused on PK, and were conducted in adults. There were a total of n=256 human subjects exposed to 1 or more doses of Ritalin LA in this development program, including n=61 adults in PK studies and n=195 children with ADHD. Of the n=195 children, n=125 received extended treatment for up to 90 days.

### 5.2.2 Adverse Event Profile for Ritalin LA

#### 5.2.2.1 Common Adverse Event Profile, Vital Signs, Weight, and Laboratory Data

The adverse event profile for Ritalin LA was similar to that known for other methylphenidate products, including notably insomnia, anorexia, and abdominal pain.

There were 2 interesting findings with regard to growth. In study 07, a 2-week trial, there was a mean increase in weight of 0.1 kg in the Ritalin LA group, compared to a mean increase in weight of 1.0 kg in the placebo group (highly statistically significant by two sample t-test). In that same study, there was a mean decrease in alkaline phosphatase of 0.9 units in the Ritalin LA group, compared to a mean increase in alkaline phosphatase of 5.4 units in the placebo group (highly statistically significant by two sample t-test).

#### 5.2.2.2 Conclusions Regarding Safety Data

Overall, there were no adverse event findings observed in the clinical trials with Ritalin LA 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. However, further explanation is needed regarding the findings regarding growth. It is known, of course, that MPH has an effect on decreasing weight increase and growth, but it seems somewhat unusual to see this in a 2-week study. There are two possible explanations related to differences in this formulation compared to the IR formulation. The interdose MPH level is higher than that seen with the IR, perhaps having a more prominent effect on noon meal consumption, and the second peak may occur much later, even at supper time, perhaps having a more prominent effect on evening meal consumption. Dr. Mosholder has asked for more detailed data displays and analyses for the weight, height, and vital signs data for study 07, and I agree. In addition, should this application ever reach an approvable status, I think we might consider asking for more long term data on growth with this formulation, out of consideration for the possibility that it may have a more prominent effect on growth because of its more variable pharmacokinetic profile.

### 5.3 Clinical Sections of Labeling

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

## 6.0 WORLD LITERATURE

There were no published papers regarding Ritalin LA submitted as part of this application.

## 7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Ritalin LA is not approved anywhere at this time.

## 8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take Ritalin LA to the PDAC.

## 9.0 DSI INSPECTIONS

DSI inspections of 2 random sites from study 07 did not reveal any deficiencies that would render the data unacceptable.

## 10.0 LABELING AND NONAPPROVAL LETTER

### 10.1 Final Draft of Labeling Attached to Non-Approval Package

Our proposed draft of labeling is attached to the nonapproval letter. As noted, we have made substantial changes to the sponsor's draft from the 11-28-00 labeling submssion.

### 10.2 Non-Approval Letter

The approvable letter includes draft labeling. While labeling is ordinarily not included in a nonapproval package, it was included here, given the fact that all parts of the application other than CMC support an approvable action, and it is possible that a decision might be made to issue an approvable letter. In addition, even if the recommendation to issue a nonapproval letter is accepted, it may be useful to provide our proposed labeling in consideration of the possibility that the CMC issue might be resolved soon.

## 11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Novartis has submitted sufficient data to support the conclusion that Ritalin LA is effective and acceptably safe in the treatment of ADHD. Nevertheless, I recommend that we issue the attached nonapproval letter, since there remain serious CMC deficiencies, as discussed. However, I also recommend that we attach our labeling proposal in order that the sponsor can begin to consider our concerns about labeling while the CMC issues are being resolved.

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

DOC: MEMRITLA.NA1

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/s/
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Thomas Laughren
9/17/01 09:15:30 AM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 21-284
SPONSOR: NOVARTIS
DRUG: RITALIN LA (EXTENDED RELEASE METHYLPHENIDATE HYDROCHLORIDE CAPSULES)
MATERIAL SUBMITTED: RESPONSE TO APPROVABLE LETTER
DATE SUBMITTED: 10-18-01
DATE RECEIVED: 10-19-01

This submission is the sponsor's response to the Division's approvable letter dated 9-28-01. Initially, this response was designated as incomplete with respect to the chemistry deficiencies cited in the approvable letter (please refer to the Division's letter of 11-01-01), but the sponsor has since provided enough information for the review clock to resume.

**Clinical issues raised in the Approvable letter**

The approvable letter included the following Clinical requests for information:

"1. Please provide a more detailed analysis of the weight data from Protocol 07; i.e., a presentation of mean weight by week of the trial, and by age and gender subgroups, along with hypothesis testing for the difference between treatment groups. In addition, descriptive statistics for vital signs, height and weight in Protocol 07E should be provided.

2. Under 21 CFR 314.50(d)(vi)(b), we request that you provide a final safety update for Ritalin LA."

**Safety Update**

Novartis reports that no new patients have been exposed in domestic or foreign studies since the 4-month safety update. Thus, there is no additional clinical trial data to report. Additionally, although Ritalin LA has been approved in Portugal, it has not been launched in any country, and so there is no postmarketing experience with Ritalin LA at this time.

**Weight and vital signs**

The sponsor provided the following additional analyses of the weight data from Protocol 07. It will be recalled that this study began with an open label Ritalin LA treatment period, designated the Titration Period, and lasting up to 4 weeks. This was followed by one week of single blind placebo, and then two weeks of randomized double blind treatment with either placebo or the subject's optimum dose of Ritalin LA from the Titration Period.

The tables below compare the mean change from baseline in weight for the Ritalin LA and placebo groups. The baseline measurements were taken at screening; i.e., before the open label titration period.

| Subgroup | Ritalin LA | Placebo |
|---|---|---|
| All Patients | | |
| N | 61 | 69 |
| Mean change from baseline, double blind week 2 (kg) | 0.12 | 0.96 |
| p-value (t-test) | 0.0001 | |

| | | |
|---|---|---|
| 6-8 years | | |
| N | 25 | 33 |
| Mean change from baseline, double blind week 2 (kg) | -0.02 | 0.61 |
| p-value (t-test) | 0.0207 | |

| 9-12 years | | |
|---|---|---|
| N | 36 | 36 |
| Mean change from baseline, double blind week 2 (kg) | 0.22 | 1.28 |
| p-value (t-test) | 0.0011 | |

| Males | | |
|---|---|---|
| N | 49 | 50 |
| Mean change from baseline, double blind week 2 (kg) | 0.23 | 0.94 |
| p-value (t-test) | 0.0025 | |

| Females | | |
|---|---|---|
| N | 12 | 19 |
| Mean change from baseline, double blind week 2 (kg) | -0.31 | 1.02 |
| p-value (t-test) | 0.0149 | |

| No previous methylphenidate use | | |
|---|---|---|
| N | 33 | 41 |
| Mean change from baseline, double blind week 2 (kg) | 0.07 | 0.93 |
| p-value (t-test) | 0.0071 | |

| Previous methylphenidate use | | |
|---|---|---|
| N | 28 | 28 |
| Mean change from baseline, double blind week 2 (kg) | 0.18 | 1.00 |
| p-value (t-test) | 0.0047 | |

With respect to our other request for information, the sponsor provided mean values from the final visit of the open label extension for pulse, blood pressure, and weight; however, the sponsor made no comparison to the baseline values. In the absence of a control group, however, even if Novartis had provided mean change from baseline data, it would be difficult to interpret.

Comment: The data show that Ritalin LA, even over the relatively short period of two weeks, produces decreased weight gain relative to placebo. This finding was consistent in every subgroup examined; i.e., older subjects, younger subjects, males, females, methylphenidate naïve subjects, and prior methylphenidate users. This confirms the finding from the original NDA review. Novartis did not object to noting this finding in the label, under Warnings/Long-term suppression of growth.

**Labeling**

In general, Novartis has accepted our proposed labeling. I will comment on a few items that are still open to negotiation.

Under Description, I do not favor including the statement, ' [redacted]
This is not helpful information; the intended effect is no guarantee that it is so.

Under Clinical Pharmacology/Pharmacokinetics, I do not favor the description [redacted] " as it is somewhat promotional in tone. In the same section under Special Populations/Age, I note that the sponsor has removed the advice about [redacted] no explanatory footnote was included, but this may be because the lowest strength available is 20 mg.

Under Precautions/Drug Interactions. Novartis has removed our statement that methylphenidate [redacted] This statement does not appear in the current Ritalin labeling, and so removing it would make the Ritalin LA and the Ritalin labels consistent, but the statement is present in the current Metadate CD labeling.

Patient Package Insert: The sponsor has made some additions to our proposed PPI. I am in agreement with most of these additions, which provide more specific information about the proper use of the drug as well as more specific precautions regarding concomitant medications. I question some of the language that Novartis has added under the heading, "How does Ritalin LA work?" as being overly promotional in tone, however. We have asked DDMAC to review the PPI.

Conclusions and recommendations: From a clinical standpoint there is no objection to approving this NDA, provided the sponsor makes the minor changes to the labeling that I have suggested above.

Andrew Mosholder, M.D., M.P.H
Medical Officer, HFD-120

Cc: Laughren, Homonnay, Mosholder