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: 29 August 2011

FROM: Mitchell V. Mathis, M.D.
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Division of Psychiatry Products, HFD-130

TO: File NDA 202-100

SUBJECT: (b) (4) Methylphenidate ER Powder (NWP06) for Suspension for the Treatment of Attention Deficit-Hyperactivity Disorder

Background and Summary

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The sponsor has demonstrated that NWP06 is safe and effective for the treatment of ADHD (b) (4)

Regulatory History

(b) (4)

. The sponsor conducted a single controlled safety and efficacy study in children and adolescents, as well as (b) (4) PK studies (b) (4)

agreed that their study, NWP06-ADD-100 appeared to demonstrate efficacy in children and adolescents with ADHD. (b) (4) .

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(b) (4)

Division of Scientific Investigation (DSI) Review
Dr. Orencia and DSI inspected and reviewed the results from both clinical sites that participated in Study NWP06-ADD-100. These were both US sites. (b) (4) .

Clinical Team Reviews
(b) (4) the sponsor has demonstrated the efficacy and safety of NWP06 in the treatment of ADHD (b) (4)

Study (b) (4)
NWP06-ADD-100 was an outpatient multicenter randomized, double blind, placebo-controlled, multiple-dose, two-treatment, crossover laboratory classroom study in 45 children ages 6-12 years with a diagnosis of ADHD. The study lasted 7 weeks and included a 4-6 week stabilization/dose-optimization phase followed by a 2-week placebo-controlled laboratory classroom crossover phase.

Appropriately diagnosed children were enrolled and dose-optimization began at 20 mg/day for all patients with titration by 10mg – 20 mg/day per week until an optimal dose was identified. The maximum permitted dose was 60 mg/day.

After optimization, patients were randomized to continue drug or placebo for a week and then these patients were assigned to the reverse treatment group in a typical crossover design. The primary efficacy endpoint was the prospectively designated mean change in SKAMP-Combined score (a generally accepted measure of ADHD symptoms used in many drug trials) at 4 hours post dose. The prospectively designated Key Secondary efficacy endpoint was onset and duration of effect as measured sequentially from 0.75 hours to 12 hours post-dose. Other secondary endpoints included the Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I), and the ADHD Rating Scale (ADHD-RS).

Findings—Efficacy
At hour 4, the SKAMP-Combined mean score for the placebo group was 19.3 and for the drug group was 7.1. LS mean difference was -12.46 ($P<0.0001$). Dr. Ritter outlines in his review that the Key Secondary efficacy findings established that NWP06 demonstrated a statistically significant treatment effect from 0.75 hours through hour 12.

Findings—Safety

There were no new or unexpected findings with this formulation compared to what is expected and labeled for other methylphenidate formulations. Common adverse reactions were decreased appetite, affective lability, insomnia, irritability, headache, dizziness, and gastrointestinal symptoms (stomach pain, diarrhea).

The mean age in this study was 8.8 years with 73% male, 27% with the inattentive subtype of ADHD, 2% with hyperactive subtype, and 71% had the combined subtype which is consistent with what is seen in clinical practice. One third of the patients had a comorbid psychiatric diagnosis, most of these (18%) had comorbid Oppositional Defiant Disorder.

Statistical Findings

(b) (4) findings of efficacy for the primary and key secondary endpoints.

Pharmacology/Toxicology

(b) (4) (b) (4)

Clinical Pharmacology/Biopharmaceutics

(b) (4). (b) (4) data from the sponsor's program were adequate to characterize the PK of NWP06 (b) (4).

There had been some concern about the CRO responsible for the PK samples and data collection, because the Office of Scientific Investigations, Office of Compliance (OSI-OC) had issued a deficiency letter on 26 Jul 2011 citing multiple areas of concern, including failure to use an adequate analytical method to measure drug concentration, falsified lab records, and other instances of misconduct. As a result, OSI-OC informed the Division that the analysis data from the CRO should be considered unreliable. Since the original problems with unreliable data were identified, the CRO has come into compliance; the sponsor had their samples (n=200) reanalyzed, and Drs. Zhang and Gobburu agree that the reassayed drug concentrations were within 3-17 percent of the original values, and so the original characterization of the PK of this product has been validated and the Office of Clinical Pharmacology (OCP) is satisfied that the data can be relied upon and that no further action is indicated in this regard.

(b) (4)

CMC Quality Issues (b) (4)

On 5 May 2011, Dr. Tele informed the Division of the findings from the inspection of the drug substance and drug product manufacturing facilities. Dr. Tele received the inspection report findings from Dr. Stock, Consumer Safety Officer in Office of Compliance (OC). These findings included incorrect amounts of materials in released batches (problem with drug product variability in filling) and discolored particulate material in the drug product; (b) (4)

(b) (4) The sponsor was able to resolve most of the CMC issues excepting the variability in filling problem (b) (4). Unfortunately, addressing this issue will require new equipment to be installed and inspected, (b) (4).

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CONCLUSIONS

The safety and efficacy of NWP06 have been established in pediatric patients with ADHD. (b) (4).

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/s/

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08/29/2011