CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202100Orig1s000

SUMMARY REVIEW

NDA 202100 Cross-Discipline Team Leader Review Memo

Date	September 13, 2012
From	Robert L. Levin, M.D.
Subject	Cross-Discipline Team Leader Review
NDA	202-100
Related IND	73-856
Sponsor	NextWave Pharmaceuticals, Inc.
Submission Date	March 30, 2012
Proprietary / Established name	QUILLIVANT Methylphenidate extended-release powder for suspension
Dosage forms / strength	Oral powder for suspension Strength (25 mg/5 mL) when reconstituted in water
Proposed Indication	Attention Deficit-Hyperactivity Disorder
Recommended Action:	Approval

1. Introduction

On July 30, 2010, the sponsor submitted NDA 202,100 to support the approval of Methylphenidate HCl Extended-Release Powder for Oral Suspension (NWP06) for the treatment of Attention Deficit-Hyperactivity Disorder. The NDA was submitted pursuant to Section 505(b)(2) of the FD&C Act. The Reference Listed Drug for this application is Methylin (methylphenidate HCl) Oral Solution (NDA 21-419). In the first review cycle, the Division concluded that the sponsor had demonstrated the efficacy and safety of the product in the treatment of ADHD. However, the Division took a Complete Response action on August 30, 2011, because there were critical, unresolved CMC issues identified on inspection of the drug product manufacturing facility. There were no other unresolved issues during the initial review cycle.

The Office of Compliance re-inspection of the drug product manufacturing facility provided the primary new data for this resubmission. The District Office and the CDER Office of Compliance have given a recommendation of Acceptable. Chhagan Tele, Ph.D. conducted the CMC review for the submission; he supports approval, based on the inspection findings and recommendations from OC. Elsbeth Chikhale, Ph.D. performed the ONDQA Biopharmaceutics review to evaluate the drug product dissolution data. Dr. Chikhale has concluded that the dissolution method and acceptance criteria are acceptable. I agree with Dr. Tele and Dr. Chikhale. There are no unresolved CMC or biopharmaceutics issues. There were no other new data in this resubmission.
I recommend approval of the NDA.

2. Background

2.1 First Cycle Facilities Inspection and Quality Issues Observed

Chhagan Tele, Ph.D. performed the CMC review in the first review cycle. Dr. Tele filed two reviews (March 23, 2011 and May 6, 2011). Dr. Tele and ONDQA did not recommend approval of NDA 202-100, because of the WITHOLD recommendation from the Office of Compliance for the drug substance and drug product sites. Dr. Tele found all of the other CMC data acceptable.

On 10 May 2011, the CDER Office of Compliance provided their recommendation of Withhold, based on the District Office's findings from the inspection at the Tris Pharma manufacturing facilities. The final recommendation from the District Office was Withhold. Marisa Stock, Consumer Safety Officer in the Office of Compliance (CDER/OC/DMPQ) outlined the findings. The NWJ District Office made the following observations upon inspection of the Tris Pharma manufacturing facilities:

1. Validation deficiencies included the following: validation times not followed; there were dissolution failures; nine batches were rejected for one product; and hold times changed in production from validated times
2. There was no justification for the sampling plan.
3. Data on two failed validation batches were excluded from the validation report.
4. There were incorrect amounts of materials in released batches.
5. Black and brown particles were observed in the drug products; this was attributed to excipients, but these excipient were still used in other batches of other products. The sponsor's investigation of the problems and the corrective action taken were inadequate.
6. The cleaning validation process was inadequate.
7. USP purified water testing was performed at (b) (4) points of use.
8. Only (b) (4) points of use were tested for water system validation.

2.2 Clinical Findings in the First Review Cycle

Efficacy Findings

Pivotal study NWP06-ADD-100) was a phase 3, outpatient, multicenter (2 U.S. sites), randomized, double-blind, placebo-controlled, two-treatment, two-period crossover laboratory classroom study of NWP06 in 45 children (ages 6-12 years) with a diagnosis ADHD. The Division decided that a single pivotal trial was sufficient, because there are extensive, accumulated efficacy and safety data for methylphenidate in the treatment of ADHD. The total duration of the study was 7 weeks. There was a 4 to 6-week open-label, dose-optimization phase, followed by a 2-week, placebo-controlled laboratory classroom, crossover phase. The primary endpoint was the change in SKAMP-Combined score at 4 hours post-dose (compared to placebo). As illustrated below, the study demonstrated the efficacy of NWP06 as measured by the change in SKAMP score.

Table 1. Primary Efficacy Results for the SKAMP-C Score at 4 hours post-dose

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
ITT population	N=39	N=39	
Mean SKAMP-C Score at 4 hours (SD)	19.3 (8.38)	7.1 (5.64)	-12.2 (7.19)
LS Mean (SE)	19.58 (1.15)	7.12 (1.14)	-12.46 (1.13)*
P-Value			*p <0.0001

The key secondary efficacy endpoints were the onset and duration of clinical effect during the classroom assessment day as measured by the change in SKAMP-C score at each post-dose time point. There was a statistically significant treatment effect at every time point assessed (0.75, 2, 4, 8, 10, and 12).

Safety Findings

There was adequate exposure to NWP06 to support the application. In efficacy study NWP06-ADD-100, there were 44 pediatric subjects treated with multiple-doses of NWP06 (20 mg, 30 mg, 40 mg, 50 mg, or 60 mg). The mean daily dose of NWP06 was 33 mg.

There were no new or unexpected findings compared to previous clinical experience with methylphenidate. There were no deaths or serious adverse events in the studies. The most commonly reported adverse events included: appetite decreased, upper abdominal pain, vomiting, diarrhea, affect lability, insomnia, irritability, logorrhea, aggression, headache, dizziness, fatigue, flushing, skin excoriation, and tic. These adverse reactions are consistent with those commonly reported in other methylphenidate studies.

2. Nonclinical Pharmacology/Toxicology

There are no new pharmacology/toxicology data in this resubmission; thus, there is no review. There are no unresolved nonclinical issues.

Dr. Elayan and Dr. Fossom have recommended several changes in labeling for the following sections: Use in Pregnancy, Use in Pediatric Patients, Mechanism of Action and Nonclinical Toxicology sections. We have incorporating these labeling recommendations

3. Chemistry Manufacture and Controls (CMC) Review – Chhagan Tele, Ph.D.

Chhagan Tele, Ph.D. performed the CMC review (filed on August 15, 2012). His review is based on the findings and recommendations of the Office of Compliance regarding the manufacturing facilities inspection. The District Office inspected the Tris Pharma, Inc. manufacturing facility in Monmouth Junction, New Jersey. They reviewed new data on the finished dosage manufacturing, the finished dose packaging, and the finished dosage

release testing for the drug product: methylphenidate hydrochloride extended-release powder (25 mg/5 mL) for oral suspension. The District Office and the CDER Office of Compliance have given an overall recommendation of Acceptable. OC issued the establishment evaluation report on June 22, 2012.

Dr. Tele has concluded that the sponsor has responded adequately regarding the CMC manufacturing deficiencies cited in the first review cycle. There are no other new CMC data to review. There are no unresolved CMC issues. I agree with Dr. Tele's conclusions and recommendations.

4. Biopharmaceutics Review

Elsbeth Chikhale, Ph.D. performed the ONDQA Biopharmaceutics review (filed on August 16, 2012). Dr. Chikhale evaluated the drug product dissolution method and acceptance criteria submitted under DMF 23870 held by Tris Pharma, Inc. In this resubmission, the sponsor submitted an updated DMF 23870; however, the Division had not identified any outstanding biopharmaceutics issues from the original NDA submission.

Dr. Chikhale has concluded that he following dissolution method and acceptance criteria are acceptable under DMF 23870:

USP Apparatus	Speed (rpm)	Volume (ml) / Temperature	Medium	Acceptance Criteria (% drug Dissolved)
II (paddle)	75	900 mL 37°C	0.4 M KH_2PO_4, pH 4.5	0.5 hr - (b) (4) 3.0 hr- 8.0 hr – NLT (b) (4)

Dr. Chikhale has concluded that all drug product dissolution method and acceptance criteria for Methylphenidate ER Powder for Oral Suspension have been resolved, and she recommends approval of the application. I agree with Dr. Chikhale's conclusions and recommendations.

In the current review, Dr. Chikhale summarized the regulatory history for NDA 202100 regarding the biopharmaceutics information submitted in the original NDA, and she summarized the original review by Angelica Dorantes, Ph.D. (filed on 3/23/11). Dr. Dorantes had reviewed the following information: 1) the originally proposed dissolution method and acceptance criteria for DMF 23870 and the sponsor's responses to the Agency's comments during the first review cycle, 2) the in vitro dose dumping study for DMF 23870, and 3) the extended-release dosage form classification. The Agency had a number of comments and requests regarding the DMF, dissolution method, and the dissolution specifications. During the first review cycle, the sponsor responded adequately to these initial deficiencies.

5. Clinical Review

Mark Ritter, M.D. performed the clinical review for the resubmission. He focused on the findings from the CMC and ONDQA/Biopharmaceutics reviewers. There were no new clinical data in this resubmission. Dr. Ritter agrees with the conclusions of Dr. Tele and Dr. Chikhale, and he recommends approval of the supplement. I agree with Dr. Ritter's conclusions and recommendations.

6. Pediatric and Maternal Health Staff Consult

The Pediatric and Maternal Health Staff reviewed the sponsor's proposed labeling for the Pediatric Use section. They have recommended the following language for Section 8.4:

> The safety and effectiveness of QUILLIVANT have been established in pediatric patients ages 6 to 17 years. Use of QUILLIVANT in pediatric patients 6 to 12 years of age is supported by adequate and well-controlled studies *[see Clinical Studies (14)]*. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of QUILLIVANT in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

PMHS has recommended that the Division explain the rationale for extrapolating the efficacy and pharmacokinetic findings from children (ages 6 to 12) to adolescents (ages 13 to 17). We have extrapolated the efficacy findings, because there is a wealth of data from numerous methylphenidate programs that demonstrate the efficacy of methylphenidate in the treatment of children and adolescents with ADHD. In addition, the disease process in ADHD and the pharmacology of methylphenidate are thought to be the same in children and adolescents. We have extrapolated methylphenidate PK findings from children to adolescents, because there are numerous PK data demonstrating that there are no significant PK differences between children and adolescents. Similarly, there is a wealth of safety data from children and adolescents treated with methylphenidate to support the use of this product in adolescents. There are no significant differences in the safety profile of methylphenidate treatment between children and adolescents with ADHD.

7. Controlled Substance Staff Consult

Steve Sun, M.D. performed the Controlled Substance Staff consult. Dr. Sun has provided expert guidance to the Division and worked closely with the review team throughout the NDA the review cycle. He has made outstanding contributions to the review of the NDA. He has advised the Division on risk management and labeling for stimulant products. In addition, Dr. Sun has provided education about numerous aspects of drug abuse and dependence that has helped the Division gain a better understanding of these issues. In his two reviews (7/19/12 and 8/16/12), Dr. Sun summarized the literature on several

topics regarding therapeutic use and illicit use of methylphenidate and amphetamine. These include: 1) stimulant studies conducted in the U.S. during the past 5 years, 2) surveys of college students regarding illicit use of stimulants, and 3) a 2009 review of data from the American Association of Poison Control's National Poison Data System.

Dr. Sun has helped develop stimulant class labeling regarding abuse and dependence. We have adopted his recommendations for the following sections of labeling: the Boxed Warning, Warnings and Precautions, Abuse and Dependence, Overdosage, How Supplied/Storage and Handling, and Patient Counseling.

Dr. Sun has recommended that the Division consider the following:

1. Request that the sponsor provide (in quarterly periodic safety reports) data and trends regarding the following types of postmarketing reports: Drug Abuse, Dependence, and Withdrawal. Request that the sponsor submit such events as 15-day expedited reports (important medical event).

Reviewer's note: We could request that the sponsor provide relevant cases in quarterly safety updates. In my opinion, it is not clear that such events would rise to the level of requiring expedited reports.

2. Request that the sponsor conduct active surveillance of the potential known and unknown methods for misuse of this new formulation of methylphenidate.

3. Request that the sponsor highlight all precautions against misuse, abuse, and diversion in any of the sponsor's materials that would be seen by patients and healthcare professionals.

4. Request that the sponsor employ safeguards against unintended distribution of the powdered methylphenidate by the pharmacist to the patient. For example, the sponsor should highlight in the instructions to the pharmacist that the drug should be reconstituted only by the pharmacist, and not to permit distribution of the product in powder form, in order to prevent the patients and caregivers from reconstituting the product.

For points 2, 3, and 4, we could discuss these recommendations with the sponsor.

8. Labeling Review

We largely focused on labeling language regarding abuse and dependence. The Controlled Substance Staff and SEALD worked closely with the Division to develop labeling language. We also made significant revisions in the sections listed below.

1. Boxed Warning for Abuse and Dependence: The new methylphenidate boxed warning for abuse and dependence is as follows:

WARNING: ABUSE AND DEPENDENCE
CNS stimulants, including QUILLIVANT, (b) (4) have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

2. Contraindications: We've deleted (b) (4)

3. Warnings and Precautions: We deleted (b) (4)

4. Adverse Reactions/Postmarketing Experience: We included postmarketing adverse events that have been reported for other methylphenidate products.

5. Drug Interactions: We deleted several drug-drug interactions, because we could not find data to support their inclusion in labeling.

6. Pregnancy: The Pediatric and Maternal Health Staff and the Pharm/Tox team revised this section using the new labeling format for the pregnancy section.

7. Pediatric Use: The Pediatric and Maternal Health Staff provided recommendations for labeling. The revised pediatric use section is as follows:

   The safety and effectiveness of QUILLIVANT have been established in pediatric ages 6 to 17 years. Use of QUILLIVANT in pediatric patients 6 to 12 years of age is supported by adequate and well-controlled studies *[see Clinical Studies (14)]*. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of QUILLIVANT in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established.

8. Drug Abuse and Dependence: We have included the recommendations of CSS.

9. Overdosage: We have included the recommendations of CSS.

10. Patient Counseling: We have included the recommendations of CSS.

We have sent our version of labeling to the sponsor.

9. Conclusions and Recommendations

In the original NDA submission, the sponsor demonstrated the efficacy and safety of methylphenidate extended-release powder for suspension in the treatment of ADHD. The only unresolved issues from the first review cycle were the deficiencies observed by the Office of Compliance upon inspection of the CMC manufacturing facilities. The District Office has re-inspected the manufacturing facilities, and they have concluded that the sponsor has responded adequately. The District Office and CDER Office of Compliance agree that the sponsor has resolved the CMC issues. OC has provided a recommendation of Acceptable, which would support the approval of the NDA. There are no unresolved issues. I recommend approval of the NDA.

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/s/

ROBERT L LEVIN
09/13/2012