CLINICAL REVIEW

Application Type	NDA
Application Number	202-100
Priority or Standard	Standard
Submission Date	30 July 2010
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Division/Office	ODE1/DPP
Reviewer Name	Mark Ritter, M.D. RPh.
Review Completion Date	1 April 2011
Established Name	Methylphenidate ER Powder
Trade Name	(Currently undetermined)
Therapeutic Class	Stimulant
Applicant	Next Wave Pharmaceuticals
Formulation	Oral Powder for Suspension
Dosing Regimen	Once Daily
Indication	Attention Deficit Hyperactivity Disorder
Intended Population	(b) (4)

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1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

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1.2 Risk Benefit Assessment

NWP06 is an extended release oral stimulant preparation (b) (4)

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2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Methylphenidate is pharmacologically classified as a stimulant. Although the exact mechanism of *in vivo* pharmacological action is not known in humans, dexmethylphenidate and methylphenidate are thought to block the reuptake of released monoamines into the presynaptic neuron, thus increasing the synaptic concentration of these monoamines in the synapse. It has been postulated that increased monoamine activity, particularly in the frontal cortex of the brain, enhances attention, focus and alertness similar to what has been observed in the 'flight or fight' response in mammalian species.

2.2 Tables of Currently Available Treatments (b) (4)

Methylphenidate was approved in 1956 for the indication of ADHD. Since the time of approval, other stimulant and non-stimulant compounds have been used to treat ADHD as shown below:

Table 1: Available Products Used to Treat ADHD

Product	Maximum daily dose
Stimulants	
Methylphenidate	60mg
Dexmethylphenidate	30mg
Amphetamine salts	60mg

Lisdexamphetamine	70mg
Non Stimulant	
Atomoxetine	100mg
Guanfacine	4mg

2.3 Availability of Proposed Active Ingredients in the United States

Methylphenidate is available in a wide variety of oral and (recently approved) dermal patch formulations with different dosing strengths. The various formulations are designed to impart different pharmacokinetic properties to extend the release of methylphenidate and deliver ADHD symptom relief through various times throughout the day.

There is currently one oral methylphenidate solution, Methylin 5mg/ml solution that is currently available in the United States. (b) (4) Methylin is an immediate release preparation of methylphenidate. (b) (4) . (b) (4) .

2.4 Important Safety Issues With Consideration to Related Drugs

The Agency has recently added cardiovascular warning language to the approved labeling for all stimulant medication products, including Focalin XR, and atomoxetine regarding patients with pre-existing cardiac abnormalities. The basis for these additional warnings stemmed from an analysis of post-marketing safety reports of sudden deaths that were seen in patients with pre-existing cardiac defects taking stimulant medications when compared to the background incidence of sudden death.

In addition, the American Heart Association[1] has recently made a class 2A recommendation to obtain ECG recordings prior to initiation to stimulant therapy. At this time, the Agency has not indicated whether additional regulatory action is or is not indicted with the stimulant class of medications.

[1] Vetter VL et al "Cardiovascular Monitoring of children and adolescents with heart disease receiving stimulant drugs: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing" *Circulation* 2008 May 6;117(18):2407-23

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2.6 Other Relevant Background Information

No other pertinent background information regarding this submission is available for this product.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

This reviewer finds no issues with the submission quality and integrity of the data contained within the submission.

3.2 Compliance with Good Clinical Practices

The studies that have been conducted under this submission appear to have been conducted with adherence with good clinical Practices.

3.3 Financial Disclosures

According to the FDA Form 3454 submitted with this NDA, none of the clinical investigators who participated in the clinical program had any financial arrangements that interfered with the outcome of the study; had a financial interest in the sponsor; or received other significant payments IAW 21 CFR 54.2 (a), (b) and (f) respectively.

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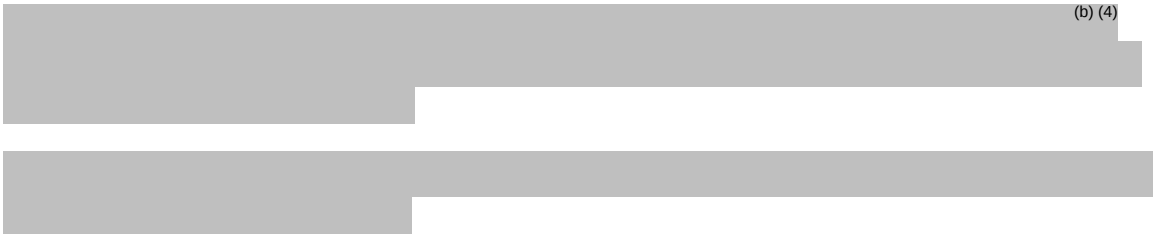
4.2 Clinical Microbiology

Not applicable for this submission.

4.3 Preclinical Pharmacology/Toxicology



4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Although the exact mechanism of *in vivo* pharmacological action is not known in humans, dexmethylphenidate and methylphenidate are thought to block the

reuptake of released monoamines into the presynaptic neuron, thus increasing the synaptic concentration of these monoamines. It has been postulated that increased monoamine activity, particularly in the frontal cortex of the brain, enhances attention, focus and alertness, similar to what has been observed in the 'flight or fight' response in mammalian species.

4.4.2 Pharmacodynamics

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4.4.3 Pharmacokinetics

Please refer to the review completed by the Office of Clinical Pharmacology (OCP) for an extensive review of the pharmacokinetics.

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Also, NWP06 can be taken with or without food.

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5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Phase 3 Studies	
NWP06-ADD-001 Dose-optimization/fixed dose	A seven week, outpatient, multicenter, double-blind, parallel-group, placebo controlled, randomized (1:1 drug: placebo), two-way, two-period (1 week each) cross-over laboratory classroom study of 45 pediatric patients (ages 6-12 years of age) with a current clinical diagnosis of attention deficit hyperactivity disorder (according to DSM-IV criteria using the K-SADS instrument) dose optimized (up to 60mg/day) according to clinical symptomatology for the first four to six weeks with double-blind dosing for 1 week with cross-over for the second week.
Phase 1 Studies	
(b) (4)	
NWP06-PPK-101	An inpatient (12 hours) , single site, open-label, single dose, two treatment (NWP06 20mg orally, NWP06 60mg orally) pharmacokinetic study of 14 children aged 6-12 and 13-17 years old (1:1) receiving either a single dose of 20mg NWP06 (4 aged 6 to 12; 3 aged 13 to 17) or 60mg NWP06 (3 aged 6-12; 4 aged 13-17)

Only safety data collected from the single dose pharmacokinetic studies will be reviewed as no clinical efficacy data was collected in either study.

5.2 Review Strategy

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5.3 Discussion of Individual Studies/Clinical Trials

Please refer to the table above.

6 REVIEW (b) (4)

(b) (4)

Efficacy was established in a single phase 3, randomized, double-blind, placebo controlled, multicenter, two-way crossover laboratory classroom study in 45 children aged 6-12 years of age who had a diagnosis of ADHD. Subjects entered an open-label, dose-optimization phase during which their dose of methlyphenidate was optimized (up to 60mg/day), prior to initiation of two weeks of double-blind, placebo-controlled treatment. The primary efficacy endpoint was the SKAMP-combined score at 4 hours post-dose between Methylphenidate treatment vs. placebo. The key secondary efficacy endpoint was the onset and duration of clinical effect as determined by scores on the SKAMP-combined scores at all time points, compared to placebo treatment. The changes from pre-dose SKAMP-combined scores were obtained, but they were secondary analyses. The primary efficacy analysis was changed (b) (4) to scores at 4 hours post-dose based on FDA comments on the statistical analysis plan (SAP) on 29 Sep 2009.

The primary efficacy analysis clearly demonstrated statistically significant reduction of SKAMP-Combined scores (i.e. improved symptomatology) at hour 4 in Methylphenidate-treated subjects as compared to placebo treatment

Table 2: Change in SKAMP Combined (SKAMP-C)score at 4 hours post dose (ITT population)

	PLACEBO N=39	METHYLPHENIDATE N=39	TREATMENT DIFFERENCE	P-VALUE
Mean SKAMP-Combined score at hour 4 (SD)	19.3 (8.38)	7.1 (5.64)	-12.2 (7.19)	
LS Mean (SE)	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)	<0.0001

6.1 Studies (b) (4)

6.1.1 Rationale for Selection of Studies for Review

(b) (4)

6.1.2 Study Summaries

Study 1

Methods/Study Design/Analysis Plan

Study NWP06-ADD-100 was conducted in 2009-2010 (b) (4) in the treatment of ADHD using a laboratory classroom setting.

The study design consisted of two distinct phases:

- Phase 1: a pre-dose screening (up to 4 weeks) to determine whether inclusion/exclusion criteria were met and to washout any previous ADHD medication use.
- Phase 2: a four-week, open-label dose optimization (flexible dose) design followed by a two week randomized, two period, double-blind, placebo controlled cross-over treatment of dose-optimized study medication or placebo (one week each). Laboratory classroom testing was performed at the end of week 4(end of open-label phase), week 5, and week 6.

INCLUSION CRITERIA
Forty (40) patients who were male or female aged 6-12 years of age with a DSM-IV diagnosis of ADHD (any type) as determined by a psychiatrist, psychologist, developmental pediatrician or pediatrician via review of K-SADS administration.

Patients were required to have an ADHD-RS score at screening OR baseline equal to or greater than the 90th percentile normalized for gender and age in at least one of the following categories:

- Hyperactive-impulsive
- Inattentive
- Total score

AND a CGI-S score of 3 or greater.

Patients must also require medication therapy or have received suboptimal efficacy, or have problems with safety and/or tolerability of current medication regimen or in need of a long acting liquid formulation.

EXCLUSION CRITERIA
The following patients were not eligible for participation in the trial:

- DSM-IV diagnoses other than ADHD or simple phobias
- Clinically significant cognitive impairment defined as an estimated IQ of 80 or less based on clinical judgment or WASI administration
- Evidence of a seizure disorder, cardiac disorder, serious cardiac conditions, glaucoma, Tourette's disorder or tics
- Any psychotropic agents other than stimulants if inclusion criteria for stimulants is met or use of atomoxetine 30 days prior to screening
- Significant laboratory deviations from normal at screening
- Positive drug test or pregnancy

DOSING
During phase 1, all subjects received an initial morning dose of 20mg of NWP06 suspension (reconstituted as 25mg/5ml). Doses were then titrated on a weekly basis by 10-20 mg based on clinical response and tolerability to a maximum dose of 60mg/day by week 4.

Once the optimized dose was determined at the end of week 4, subjects then entered the double-blind, randomized, cross-over phase of the study.

EFFICACY ENDPOINT
The primary efficacy endpoint for this study (b) (4) using the laboratory classroom setting and serial administrations of the SKAMP-Combined rating scale. Based on FDA comments on the statistical analysis plan on 29 Sep 2009, the sponsor changed the endpoint from (b) (4)" to "SKAMP-combined score at 4 hours". (b) (4)

In addition, two key secondary efficacy variables that were measured were modified from:

(b) (4)

To:

1. Onset of efficacy of action was determined at 0.75 hrs post dose if the difference between the two treatments was statistically significant (p<=0.05) at that time point.
2. If the difference between the two treatments was statistically significant (p<= 0.05) at the 0.75 hour time point, the duration of efficacy was claimed at the last time point at which the difference was still statistically significant.

STATISTICAL ANALYSIS PLAN
The original statistical analysis plan proposed the following analyses to be conducted:

However, previous internal Agency discussions identified potential issues with using (b) (4) (b) (4). In order to correct for this effect, the FDA provided comments on the SAP to the sponsor on 29 Sep 2009 which were adopted by the sponsor. The sponsor proposed the following analysis strategy:

- The primary efficacy analysis will be based on the SKAMP-Combined scores at 4 hours post dose, (b) (4)
- Secondary efficacy analyses will be based on observed scores at each time point (b) (4)
- The onset of effect was assessed at the 0.75 hr time point. (b) (4)

(b) (4)

The duration of efficacy will be determined as the last consecutive time point at which the difference between the two treatments was statistically significant

- ANOVA will be used with subject within sequence as a repeated effect.

Results

Demographics and Baseline Characteristics

In general, the patients who participated in this trial were aged 8.8 years of age, male (73%) and white (78%).

The majority of children had the combined subtype of ADHD (71%), and 27% had the inattentive subtype. Most children had a diagnosis of ADHD without a history of co morbid psychiatric disorders (69%). However, in patients who had a co morbid psychiatric diagnosis, oppositional defiant disorder was the most prevalent (18%)

Table 3: Demographics and Baseline characteristic of the Safety population (N=45)

CHARACTERISTIC	VALUE (SD)
Age (y)	8.8 (1.69)
Male	73%
White	78%
ADHD-Combined type	71%
ADHD-inattentive	27%
No psychiatric co morbidity	69%
Co-morbid ODD	18%

Patient Disposition
A total of 45 patients were randomized to treatment in the study. Six (6) patients discontinued from the study during the open-label phase of the protocol prior to double-blind treatment, as illustrated in the table below:

Table 4: Disposition of Patients who Prematurely Discontinued the Trial

REASON FOR DISONTINUATION	N
Withdrawal of Consent/Assent	2
Adverse Event	2
Lack of efficacy	1
Lost to follow-up	1
Total	**6**

Adverse events that led to discontinuation were affect lability (in one patient 18 days after study medication administration) and aggression/temper tantrum (in another patient on day 9 of study medication administration). In both cases, the adverse events resolved within one day and no long-term clinical sequelae were reported. Both adverse events are consistent with known adverse events associated with stimulant medication, (b) (4)

Concomitant Medication Use

Most patients (84% 31/45) took at least one concomitant medication during the study. Topical dermatological preparations were the most commonly administered concomitant medications (60%), followed by antihistamines (20%) and analgesics (20%). In view of the pharmacological actions of these concomitant medications, it is unlikely that the use of these medications substantially affected the results of the efficacy analysis or safety/tolerability of the study medication.

Table 5: Concomitant medication use (N=45)

MEDICATION	PROPORTION
Topical antipruritics	60%
Systemic antihistamines	20%
Analgesics	20%
Multivitamins	13%
Anti-inflammatory	7%
Inhales B2 agonists	4%
Vitamin C	4%
Beta lactam antibiotics	4%
Expectorants	2%
Oral cold preparations	2%
Psycho Stimulants	2%
Stomatological preparations	2%
Viral vaccines	2%
Scabacides	2%
Posterior Pituitary Hormones	2%

Important Protocol Violations

Ten patients (22%) had documented treatment deviations. In addition, 3 patients (7%) did not have PK samples collected. The sponsor did not specify which "treatment deviations" occurred or how severe the effect of these deviations may have had on clinical efficacy results.

Because of the large treatment effect observed, it is unlikely that the unspecified treatment deviations would have changed the efficacy or safety results of this study.

Dosing
The overall mean length of exposure to NWP06 was 41 days: 28.8 days in the open label phase and 13.8 days in the double blind portion of the study.

The mean daily dose of NWP06 during the study was 32.8mg.

Efficacy Results

Primary Efficacy

The results of the primary efficacy analysis demonstrated a statistically significant change in SKAMP scores at the 4 hour time point in the NWP06 treated subjects compared to placebo treatment:

Table 6: Change in SKAMP Combined (SKAMP-C)score at 4 hours post dose (ITT population)

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 <0.0001

(b) (4)

Conclusions

Efficacy at the 4 hour pot-dose time point was clearly established when compared to placebo.

6.1.3 Crosscutting Issues

Subgroup Analyses

The sponsor performed additional analyses by site, final dose (20mg, 30/40mg, and 50/60mg), age, gender, ADHD type, and ADHD baseline severity. In addition, efficacy by treatment sequence was evaluated by the Agency.

Site Analysis
Both sites demonstrated a statistically significant treatment decrease in SKAMP-C scores as compared to placebo

Table 8: Change in SKAMP-C Score at 4 hours post dose by site (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Site One N=26			
Mean SKAMP-C Score at 4 hours (SD)	20.3 (7.56)	7.0 (4.77)	-13.2 (7.35)
LS Mean (SE)	20.48 (1.21)	7.02 (1.21)	-13.45 (1.35) *
Site Two N=13			
Mean SKAMP-C Score at 4 hours (SD)	17.3 (9.84)	7.2 (7.30)	-10.2 (6.67)
LS Mean (SE)	17.63 (2.54)	7.5 (2.54)	-10.13 (1.99)**

* $p<0.0001$; **$p=0.0003$

Age
Consistent with the primary efficacy results, a decrease in SKAMP-C scores were observed in each age group at the 4 hour time point.

In patients aged 6-7, efficacy was not established past the hour 8 time point. In subjects aged 11-12, efficacy was not demonstrated past the 10 hour time point. However, because there were a small number of subjects in each of these age groups and there were wide variations seen in results, it is difficult to interpret these findings. Additional studies are recommended to be conducted to confirm this finding.

Table 9: Change in SKAMP-C Score at 4 hours post dose by age (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Age 6-7 N=7			
Mean SKAMP-C Score at 4 hours (SD)	24.7 (10.36)	8.9 (9.67)	-15.9 (7.10)
LS Mean (SE)	25.38 (3.45)	9.71 (3.45)	-15.67 (2.91)*
Age 8-10 N=23			
Mean SKAMP-C Score at 4 hours (SD)	18.7 (6.78)	5.5 (3.36)	-13.3 (7.03)
LS Mean (SE)	19.02 (1.08)	5.30 (1.08)	-13.73 (1.30)**
Age 11-12 N=9			
Mean SKAMP-C Score at 4 hours (SD)	16.4 (9.53)	9.8 (5.63)	-6.7 (4.74)
LS Mean (SE)	16.58 (2.79)	9.83 (2.79)	-6.75 (1.68)***

*** p=0.003; **p <0.0001' ***p=0.0050**

Gender

A statistically significant reduction in SKAMP-C scores was seen at the 4 hour time point for both sexes. With the exception of females not demonstrating a statistically significant effect past hour 10, there were significant decreases in scores at all other time points.

Table 10: Change in SKAMP-C Score at 4 hours post dose by gender (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Male N=28			
Mean SKAMP-C Score at 4 hours (SD)	19.3 (8.62)	8.5 (5.99)	-10.9 (6.36)
LS Mean (SE)	19.92 (1.40)	8.69 (1.40)	-11.24 (1.20)*
Female N=11			
Mean SKAMP-C Score at 4 hours (SD)	19.2 (8.13)	3.5 (2.21)	-15.6 (8.33)
LS Mean (SE)	19.05 (1.87)	3.57 (1.87)	-15.48 (2.60)**

* p<0.0001; **p=0.0002

ADHD subtype

A treatment effect was observed in patients with either the inattentive or combined ADHD subtype.

In the inattentive subgroup, no statistically significant change in SKAMP-C scores was seen past 10 hours post dose.

Table 11: Change in SKAMP-C Score at 4 hours post dose by ADHD-Subtype (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Inattentive N=11			
Mean SKAMP-C Score at 4 hours (SD)	16.5 (7.12)	7.4 (4.20)	-6.1 (4.48)
LS Mean (SE)	13.30 (1.80)	7.25 (1.80)	-6.05 (1.42)*
Combined N=27			
Mean SKAMP-C Score at 4 hours (SD)	21.4 (7.86)	7.0 (6.28)	-14.3 (6.61)
LS Mean (SE)	22.12 (1.29)	7.24 (1.29)	-14.88 (1.18)**

*** p=0.0021; **p <0.0001**

ADHD-Severity at baseline

Regardless of baseline ADHD severity on the SKAMP-C combined score (at or below median severity; above median severity), NWP06 treatment resulted in a decrease in SKAMP-C scores. Even in patients with less severe symptoms, a greater than 50% reduction in SKAMP-C scores was still observed at 4 hours post dose with onset at 0.75hr.

Table 12: Change in SKAMP-C Score at 4 hours post dose by ADHD-Severity at baseline (ITT population)

STATISTIC	PLACEBO (N=44)	NWP06 (N=44)	DIFFERENCE
Equal/Below Median N=20			
Mean SKAMP-C Score at 4 hours (SD)	14.8 (7.15)	5.8 (3.75)	-9.0 (6.77)
LS Mean (SE)	14.58 (1.37)	5.54 (1.37)	-9.13 (1.63)*
Above Median N=19			
Mean SKAMP-C Score at 4 hours (SD)	24.1 (6.88)	8.5 (6.95)	-15.6 (6.12)
LS Mean (SE)	23.88 (1.52)	8.43 (1.52)	-15.45 (1.32)**

*** p<0.0001; **p <0.0001**

Dose Response

Potential dose-response relationships cannot be determined from this dose-optimization study, because subjects were not randomized to fixed-dose treatment arms.

Key Secondary Variables

With regard to the key secondary endpoint of onset and duration of effect, NWP06 treatment demonstrated a statistically significant effect on mean SKAMP-C scores at every time point measured, compared to placebo treatment:

Table 13: Least Square Mean Change in SKAMP Combined (SKAMP-C)score at all time points measured post dose (ITT population)

TIME POST DOSE (HR)	LS MEAN SKAMP-C SCORE (SE) PLACEBO	LS MEAN SKAMP-C SCORE (SE) NWP06	DIFFERENCE (SE)	P-VALUE
0.75	16.16 (1.00)	9.84 (1.00)	-6.32 (1.09)	<0.0001
2	17.28 (1.01)	7.31 (1.01)	-9.98 (1.02)	<0.0001
4	19.58 (1.14)	7.12 (1.14)	-12.46 (1.13)	<0.0001
8	20.41 (9.33)	10.8 (8.23)	-9.33 (1.28)	<0.0001
10	18.29 (1.37)	14.50 (1.37)	-3.79 (1.11)	0.0016
12	20.26 (1.58)	15.49 (1.58)	-4.77 (1.40)	0.0016

Key Secondary efficacy analyses were similar in the per-protocol population, with all time points showing statistically significant decreases in SKAMP-C scores at all time points tested in the NWP06 group vs. placebo.

Long-Term Efficacy

Long-term efficacy was not evaluated (b) (4).

7 REVIEW OF SAFETY

Safety Summary

NWP06 was well tolerated by most patients. Adverse events that occurred in the trial are consistent with known adverse events associated with methylphenidate administration (b) (4)

No deaths or serious adverse events occurred during this trial. Two patients were withdrawn because of severe adverse events: aggression/temper tantrum and affect lability. These adverse events were associated with methylphenidate treatment. (b) (4) Both patients fully recovered.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data that was obtained from the one clinical efficacy study was reviewed.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the most current version of MedDRA.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

No pooling of data was performed because only one clinical study was conducted.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For study NWP06-ADD-100, the overall mean length of exposure to the study medication was 28.8 $\pm$4.60 days in the open-label optimization phase and 13.8 $\pm$0.45 days in the double blind phase. The average daily dose of NWP06 was 32.8 $\pm$7.82 mg.

Please refer to section 6.1.2 for a review of the patient demographics for study NWP06-ADD-100.

7.2.2 Explorations for Dose Response

Dose-response relationships for adverse events cannot be determined, because subjects were not randomized to fixed doses.

7.2.3 Special Animal and/or In Vitro Testing

(b) (4)

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7.2.4 Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

(b) (4)

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the clinical development program of this NDA.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs) that occurred during the clinical trial.

7.3.3 Dropouts and/or Discontinuations

There were two (2) patients who were discontinued from the study secondary to adverse events that occurred during the open-label phase (dose optimization) trial:

Subject 02-006: an 8 yo male who was discontinued at day 18 for adverse event of affect lability

Subject 02-016: a 6 yo male who was discontinued on day 9 for adverse event of temper tantrum/aggression

As these adverse events occurred prior to the double-blind treatment phase, these discontinuations had no impact on the efficacy results. In addition, both adverse events have been commonly associated with use of stimulants (b) (4)

7.3.4 Significant Adverse Events

There were no significant or unusual adverse events that occurred in this trial.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission-specific primary safety concerns.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events that occurred during the double-blind, placebo controlled study are consistent with the labeling of the reference listed product. Due to the dose optimization study design, dose-response relationships for adverse events cannot be evaluated in this study

Table 14: Adverse Events occurring during the double blind cross-over phase (safety population) N=45

Adverse event	Placebo	NWP06
Affect lability	4%	7%
Upper abdominal pain	2%	2%
Aggression	2%	-
Initial insomnia	-	2%
Stereotypy	2%	-
Tic	-	2%
Vomiting	-	2%
Motion Sickness	-	2%
Eye pain	-	2%
Decreased Appetite	-	2%

7.4.2 Laboratory Findings

Clinical laboratory testing was performed only at baseline in this study. Therefore clinical laboratory changes over time with study medication use cannot be determined in this study.

Current stimulant labeling does not indicate clinically significant laboratory changes with use over time. Based on review of stimulant class labeling and literature review examining laboratory changes with stimulant use, this reviewer feels that no additional testing is indicated.

7.4.3 Vital Signs

There were small mean changes from baseline to week 2 in systolic and diastolic blood pressure. These changes are consistent with the known effects of stimulant administration (b) (4)

7.4.4 Electrocardiograms (ECG's)

ECGs were performed only at baseline in this study. Therefore ECG changes over time with study medication use cannot be determined in this study.

Current stimulant labeling does not indicate clinically significant ECG changes with use over time. Based on review of stimulant class labeling and literature review to examine ECG changes with stimulant use, this reviewer feels no additional testing is indicated.

7.4.5 Special Safety Studies/Clinical Trials

No additional safety studies or special safety studies were conducted with this NDA.

7.4.6 Immunogenicity

Immunogenicity studies were not performed as (b) (4)

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency of adverse reactions cannot be determined form this study, because patients were dose-optimized prior to double-blind treatment. No fixed dose clinical efficacy assessment was performed.

7.5.2 Time Dependency for Adverse Events

Based on the short term adverse event data that was collected in the double-blind study, adverse events did not appear to be related to duration of treatment exposure. However a full analysis of time dependent adverse events could not

be performed as there were no long-term controlled data that was collected during the clinical development program.

7.5.3 Drug-Demographic Interactions

There were no explorations done to examine drug-demographic interactions in the clinical development program. Also, as the number of subjects enrolled in the clinical study was small, such an analysis would have limited power to detect any interactions if such interactions existed.

7.5.4 Drug-Disease Interactions

No additional studies were performed in patients with clinically significant medical illnesses.

7.5.5 Drug-Drug Interactions

There were no explorations done to examine drug-drug interactions in the clinical development program.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

7.6.3 Pediatrics and Assessment of Effects on Growth

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

(b) (4) During the clinical development program for NWP06, there were no intentional or unintentional cases of overdose in patients who received NWP06.

7.7 Additional Submissions/Safety Issues

(b) (4)

Study NWP06-PPK-101

No deaths or SAEs were reported in this study. There were no discontinuations due to adverse events. Three (3) patients experienced an adverse event during this trial:

- Patient 002 (6-12 yo group 60mg) experienced a transient mild episode of presyncope during a screening blood draw.

- Patient 011 (6-12 yo group 20mg) experienced a mild episode of presyncope during a PK blood draw.
- Patient 003 (6-12 yo group 60mg) experienced vomiting 2 hours after receiving the study medication.

(b) (4)

9 APPENDICES

9.1 Literature Review/References

No literature reviews were performed or reviewed as part of this NDA review, because the safety and efficacy of methylphenidate has been well-established.

(b) (4)

9.3 Advisory Committee Meeting

An advisory committee meeting was not scheduled for this NDA.

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/s/

MARK A RITTER
04/01/2011

ROBERT L LEVIN
04/07/2011

(b) (4)