

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

DATE: Nov. 3, 2014

FROM: Jing Zhang, MD. PhD.
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HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 22037/S-10

**Proprietary/
Established name:** Intuniv/Guanfacine Extended Release Tablet

**Dosage forms/
Strength:** Oral Tablets: 1, 2, 3, and 4 mg

Indication: Attention deficit/hyperactivity disorder in children and adolescents
aged 6 to 17 years old

Recommendation: Approval

I. Introduction and Background

INTUNIV, an oral guanfacine hydrochloride extended release formulation, is a selective central α_2 agonist. Its mechanism of action in Attention Deficit/Hyperactivity Disorder (ADHD) is not known; however, preclinical data suggests it acts centrally by stimulating post-synaptic α^2 adrenoreceptors located in the locus coeruleus (midbrain) and the prefrontal cortex by modulating the levels of norepinephrine. As an immediate release (IR) tablet formulation, guanfacine has been used as an antihypertensive agent for over 20 years. Shire initiated IND 63,551 on Oct. 26, 2001 to develop guanfacine HCL ER (INTUNIV) for indication of ADHD. On September 2, 2009, INTUNIV was approved by FDA as mono-therapy for ADHD in children and adolescents aged 6-17 years. Subsequently, Intuniv was approved as adjunctive therapy to psycho-stimulants in children and adolescents aged 6-17 years on February 25, 2011.

At the time of approval for the indication of treatment of ADHD in children and adolescents aged 6-17 years on September 2, 2009, FDA asked the sponsor to conduct a confirmative adolescent study (for patients ages 13 -17, PMC 1538-2) as a post marketing commitment

because the studies that were basis for the NDA approval failed to demonstrate efficacy in adolescent subgroup, most likely due to less than optimal exposure. Subsequent to the NDA approval, FDA issued a pediatric written request (WR) on April 1, 2011 for a pediatric study to evaluate the treatment of ADHD in adolescent patients ages 13 to 17.

To satisfy PMC 1538-2 and the pediatric written request, the sponsor conducted Study SPD503-312, a double-blind, randomized, multicenter, placebo-controlled study to evaluate the efficacy and safety of INTUNIV in adolescents aged 13-17 years with a diagnosis of ADHD when given at doses up to 7 mg per day using a flexible dose optimization design.

This submission included study reports from Study SPD503-312 and SPD503-316. Study SPD503-316 conducted to meet European regulatory requirement, is an additional short-term, randomized, double blind, placebo-controlled study using a flexible dose (up to 7 mg) optimization design in children and adolescents aged 6-17 years with a diagnosis of ADHD. The study was included to provide additional supportive evidence.

II. Summary of Conclusions and Recommendations from Review Teams

1. CMC

The supplement does not provide for any changes to the drug product, manufacturing process, or specifications and there are no CMC-related labeling changes. The sponsor submitted a categorical exclusion claim and stated that they have no knowledge of any extraordinary circumstances which exist that would require additional controls to be imposed on the use of guanfacine in order to protect the environment. Our CMC review team felt that the claim of categorical exclusion is acceptable.

2. Nonclinical Pharmacology/Toxicology

INTUNIV is an approved drug. There are no unresolved nonclinical pharmacology/toxicology issues for this application.

3. Clinical Pharmacology/Biopharmaceutics

Praveen Balimane, PhD is the clinical pharmacology reviewer for this submission. His analyses focused on the new dose proposed by the sponsor. In the previous approved label, INTUNIV dose is body weight based and can be given up to 4 mg/day. In the current submissions, the sponsor intended to increase the dose limit to 7mg/day. Dr. Balimane's analyses found that the new higher dose of 7 mg/day in adolescents is acceptable for the following reasons:

- INTUNIV's pharmacokinetics is known to be weight-based with higher exposures in children (6-12 years) compared to adolescents (13-17 years). The exposures in children with a given dose were roughly 40% higher than that in adolescents. The exposure in adolescents at 7 mg dose is expected to be similar to the exposure in children taken 4 mg dose. This was confirmed by Population PK data obtained from study SPD503-312.

- In two flexible dose studies, Study SPD503-315 (a flexible dose relapse prevention study) and SPD503-316, it was observed that percentage of adolescents reaching the higher maintenance dose of 5-7 mg was “similar” to the percentage of children reaching the maintenance dose of 4 mg. This provides evidence that in adolescents a higher dose (5-7 mg) is tolerated and required for efficacy as compared to 4 mg dose level in children.

4. Clinical

The clinical data from this application was reviewed by Jenn Sellers MD, a medical reviewer. Andrejus Parfionovas PhD is the statistical reviewer for this submission. Please refer to their reviews for more detailed review information.

Study SPD503-312

Study Design

Study SPD503-312 was a multicenter, randomized, double-blind, placebo-controlled, flexible dose optimization study designed to assess the efficacy and safety of once daily dosing with INTUNIV (SPD503) at doses up to 7mg per day as monotherapy compared with placebo in adolescents aged 13-17 years with diagnosis of ADHD. The study was conducted from 09/19/2011 to 05/16/2013 at 52 sites in the US.

The study included 5 periods: Screening, Dose Optimization (7 weeks), Dose Maintenance (6 weeks), Dose Tapering (2 Weeks), and Follow-Up Period. Eligible subjects were randomized to either SPD503 or placebo at a 1:1 ratio. Allocation of treatment was stratified within each weight group (34.0-41.4, 41.5-49.4, 49.5-58.4, and 58.5-91.0kg). All subjects initially received 1mg/day of SPD503 or placebo and doses were gradually titrated up to the maximum dose permitted for the subject’s respective weight group (6 to 12 years up to 4 mg/d, 13 to 17 years up to 7 mg/d) with incensement of 1 mg after a minimum of 1 week. Optimal dose was defined as at least 30% reduction in ADHDRS-IV total score from Baseline Visit and a CGI-I of 1 or 2 at a given tolerated dose. All subjects were maintained at their optimal dose for 6 weeks during Dose Maintenance Period and followed by 2 weeks Dose Tapering Period.

There were no clinically significant differences between the treatment groups for demographic and baseline disease characteristic. The majority of subjects were male (64.7%), non-Hispanic (78.8%), and white (72.8%), which were consistent with the prevalence of ADHD (2 times more common in male than in female) and the ethnic profile where the study was conducted. The mean age of subjects was 14.5 years.

A total of 314 subjects were randomized, 207 completed the study, and 312 were included in the full analysis set. The completion rate at the endpoint (the last visit before taper) was 74.5% and 70.1% for SPD503 and placebo, respectively. More subjects withdrew the study due to adverse event in SPD503 vs. placebo treatment (5.7% vs. 1.9%, respectively) and more subjects withdrew due to lack of efficacy in placebo vs. SPD503 treatment (15% vs. 5.7%, respectively).

Efficacy findings

The primary efficacy outcome measure was the mean change from baseline to endpoint in the clinician completed ADHD-RS-IV total score. The secondary efficacy outcome measure included the clinical global impressions (CGI-S) Scale (key secondary endpoint) and Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P) Learning and School Domain and Family Domain at the endpoint.

The primary efficacy measurement was analyzed by a last observation carried forward (LOCF) ANCOVA.

There was a statistically significant difference between the treatment groups in favor of SPD503 ($p < 0.001$) in the adjusted mean change from baseline to endpoint in the ADHD-RS-IV total score. The following table summarized the primary efficacy findings of Study SPD503-312.

Table 1: Summary of MMRM Analysis of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Week 13 (FAS) - Study SPD503-312

	Placebo (N=155)	SPD503 (N=157)
Baseline		
N	155	157
Mean (SD)	40.0 (6.11)	39.9 (5.57)
Visit 13		
N	106	109
Mean (SD)	20.3 (13.35)	14.1 (9.38)
Change from baseline		
Mean (SD)	-19.5 (12.63)	-25.7 (10.09)
Comparison to placebo ^a		
LS mean	-18.527	-24.552
Difference in LS means	NA	-6.026
(95% CI)	NA	-8.865, -3.187
Effect Size	NA	0.52
p-value		<0.001

^a LS Mean, standard error (SE), effect size, and p-value are based on repeated measures analysis for the change from baseline scores at Visits 3-

13 (Weeks 1-13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (11 levels), treatment group-by- time, and weight group (4 levels) as fixed effects and including baseline and base line by- time as covariates. Note: A negative difference in LS Mean (SPD503 - placebo) indicates a positive effect of the active treatment over the placebo.

ADHD-RS-IV=Attention deficit/Hyperactivity Disorder Rating Scale-IV; CI=confidence interval; FAS=Full Analysis Set;

LS=least squares; MMRM=mixed model repeated measures; NA=not applicable; SD=standard deviation

Source: Study Report Body page 83/2098

The sponsor performed sensitive analysis on the change from baseline in ADHD-RS-IV total score using pattern mixture model. The results were consistent with the primary analysis.

An analysis on the key secondary endpoint, the dichotomized CGI-S score, also showed statistically significant difference in favor of SPD503 treatment ($P < 0.01$).

Our statistical reviewer, Andrejus Parfionovas PhD, confirmed the sponsor's analysis results on the primary end point and he also conducted an explorative subgroup analysis on gender, race and ethnicity was performed by our statistical reviewer. No subgroup analysis on age and region was performed because it was an adolescent and a US study. The reviewer did not find substantial heterogeneity in treatment efficacy among the subgroups.

Study SPD503-316

Study Design

Study SPD503-316 was conducted from Jan 17, 2011 to May 01, 2013 at 58 sites, including 11 sites in the United States (US), 2 sites in Canada, and 45 sites in Europe (Austria, France, Germany, Ireland, Italy, Poland, Romania, Spain, Sweden, Ukraine, and United Kingdom).

The study design of SPD503-316 was similar to that of SPD503-312, which is a multicenter, randomized, double-blind, placebo-controlled, flexible dose optimization study. The study included a Screen, a Dose Optimization (4 - 6 weeks) and Dose-maintenance (6 weeks), a Dose Tapering (2 weeks) and a Follow-up Period. The differences were 1) study SPD503-316 included both children (6-12 years) and adolescents (13 to 17 years); 2) there was an active control arm (Strattera); and 3) the dose optimization period was 4 weeks for children (ages 6-12, maximum dose 4 mg/d) and 6 weeks for adolescents (ages 13-17, maximum dose 7 mg/d based on baseline weight). The criteria used for defining optimal dose, the dose titration and dosing schedule were same as that in study SPD503-312.

Eligible subjects were randomized 1:1:1 ratio to placebo, SPD503, or Strattera. Allocation to treatment was stratified within age group (6 to 12 years and 13 to 17 years) and country.

For Strattera, in children and adolescents weighed <70kg, dosing was initiated with approximately 0.5mg/kg/day, increased to target dose—approximately 1.2mg/kg/day after at least 1 week based on tolerability, and not exceeded 1.4mg/kg/day. Dosing in those weighed \geq 70kg was initiated at 40mg/day and increased to 80 mg/d after a minimum 1 week based on tolerability, and not exceeded 100mg/day.

There were no clinically significant differences between the treatment groups for demographic characteristics (age, gender, race, ethnic group, and BMI) and baseline disease characteristics. Of the 337 subjects in the Fall Analysis Set (FAS)/Safety Population, 71.8% were in the 6-12 year age group and 28.2% were in the 13-17 year age group. The mean age of subjects was 10.8 years (ranged 6-17 years).

A total of 338 subjects were enrolled and 272 subjects completed the study (82.9% in placebo, 79.1% in SPD503, and 79.5% in Strattera, respectively). The number of subjects withdrew due to lack of efficacy was higher in the placebo group (12.6% in placebo, 4.3% in SPD 503, and 4.5% in Strattera, respectively) and the number of subjects withdrew due to AEs was higher in the SPD503 group (0.9% in placebo, 7.8% in SPD503, and 4.5% in Strattera).

Efficacy Findings

The primary efficacy outcome measure was the mean change from baseline to endpoint (end of 10 week for children, 6-12 years, and 13 weeks for adolescents, 13-17 years) in clinician completed ADHD-RS-IV total score. The secondary efficacy outcome measure included the clinical global impressions (CGI) Scale and the WFIRS-P functionality assessment at the endpoint.

The primary efficacy measurement, the ADHD-RS-IV total score, was analyzed by a last observation carried forward (LOCF) ANCOVA.

There was a statistically significant difference between the treatment group of SPD503 ($p < 0.001$) and placebo in the adjusted mean change from baseline to endpoint in the ADHD-RS-IV total score. Strattera also had a greater improvement from baseline compared with placebo (nominal $p = 0.017$). The table following summarized the primary analysis of the primary end point.

Table 2: Summary of ADHD-RS-IV Total Score and Change from Baseline in ADHD-RS-IV Total Score at Visit 15 (Week 10/13) (LOCF) (FAS), Study SPD503-316

	Placebo (N=111)	SPD503 (N=114)	STRATTERA (N=112)
Baseline			
n	111	114	112
Mean (SD)	43.2 (5.60)	43.1 (5.47)	43.7 (5.86)
Visit 15 (Week 10/13)			
n	111	112	112
Mean (SD)	28.1 (14.13)	19.2 (11.85)	25.0 (12.97)
Change from baseline			
Mean (SD)	-15.0 (13.07)	-23.9 (12.41)	-18.6 (11.91)
Comparison to placebo ^a			
LS mean	-15.0	-23.9	-18.8
Difference in LS means	NA	-8.9	-3.8
95% CI	NA	-11.9, -5.8	-6.8, -0.7
Effect size	NA	0.76	0.32
p-value		<0.001	0.017 ^b

^a LS mean and standard error, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group, age group, and country as fixed effects, and baseline value as a covariate. ^b Nominal p-value uncorrected for multiplicity.

Note: A negative difference in LS Mean (active treatment - placebo) indicates a positive effect of the active treatment over the placebo. The primary analysis is the SPD503 vs. placebo comparison at Visit 15 (Week 10/13).

ADHD-RS-IV=Attention-deficit/Hyperactivity Disorder Rating Scale IV; ANCOVA=analysis of covariance; CI=confidence interval; FAS=Full Analysis Set; LOCF=last observation carried forward; LS=least squares; NA=not applicable; SD=standard deviation. Source: Study Report Body page 87/2899

The sponsor has also performed analysis of the secondary efficacy endpoint dichotomized CGI-I score at end point (Week 10/13) using CMH test stratified by weight group to examine treatment group effects. The results also showed statistically significant difference in favor of SPD503 treatment ($P < 0.01$).

Our statistical reviewer, Andrejus Parfionovas PhD, confirmed the sponsor's analysis results on the primary end point and he also conducted an exploratory subgroup analysis on gender, age group, race, ethnicity and geographic region. There was no substantial heterogeneity in treatment efficacy among the subgroups. Although the observed treatment effect in the adolescent subgroup was almost twice smaller than that in the children subgroup (-4.74 in adolescents, and -10.49 in children), the results from both age subgroups still suggest the efficacy of SPD503 compared to placebo. The only subgroup that had opposite sign (1.56) for numeric estimate for the efficacy effect was the Black/African American subgroup of patients. The reason for the inconsistency could possibly be attributed to the relatively large variance in quite a small subgroup (n=14).

In summary, both Dr. Sellers and Parfionovas agreed that both Study SPD503-312 and -316 have demonstrated that INTUNIV® (Guanfacine HCl) was statistically significantly superior to placebo (p-value < 0.001 for both studies) in reducing the symptoms of ADHD measured by the mean change from baseline to endpoint in the ADHD-RS-IV total score in pediatric patients 6 to 17 years of age.

SAFETY REVIEW

The safety review mainly focused on Study SPD503-312. The safety review on Study SPD503-316 is relatively brief because the safety of SPD503 had been systemically reviewed in children and adolescent population in the original NDA review and in the review for Study SPD503-312. Due to different study populations, these two studies were not pooled for safety analyses.

Study SPD503-312

A total of 157 subjects were exposed to SPD503 in Study SPD503-312. The mean exposure was 89.9 days. The mean optimal dose for the SPD503 treatment group was 4.3 mg. The majority received optimal doses of 3, 4, 5, or 6mg (22.9%, 19.8%, 20.6%, or 18.3%, respectively). The mean weight-adjusted optimal dose was 0.073mg/kg, with most subjects optimized at 0.05-0.08mg/kg (49.6%) or 0.09-0.12mg/kg (35.9%).

No deaths reported in Study SPD503-312. Four subjects receiving SPD503 and 2 subjects receiving placebo experienced a Serious Adverse Event (SAE). The SAEs reported in SPD503 group were vomiting and withdrawal hypertension (1), cholecystitis chronic and abdominal pain (1), homicidal ideation (1) and loss of consciousness and concussion (1). Withdrawal hypertension and abdominal pain are labeled adverse events. The rest SAEs were judged not drug related by our clinical reviewer.

Nine subjects (5.7%) receiving SPD503 and 3 subjects (1.9%) receiving placebo had a treatment emergent adverse events (TEAEs) leading to discontinuation from the study. Twenty one subjects (13.4%) receiving SPD503 and 8 subjects (5.2%) receiving placebo had a TEAE(s) leading to dose reduction. Among the 9 SPD503 subjects who had TEAEs leading to discontinuation, only 1 adverse event (AE), Wolff-Parkinson-White syndrome, was not a labeled AE and it seemed not drug related.

The common AE profile in Study SPD503-312 was consistent with the established SPD503 safety profile. Even though the study used a higher maximum dose, up to 7 mg/d, the rate of common AEs, such as somnolence, hypotension and dizziness, were not worse than that in previous controlled studies with lower doses in the same populations. The possible explanations could be 1) gradually dose titration minimized AEs, and 2) weight based dosing—the patients who got higher dose in adolescents, more than 4 mg/d, did not have higher drug exposure because of SPD503's PK profile.

The common AEs, which had occurred $\geq 5\%$ and at least twice placebo rate, included somnolence (54%), insomnia (11%), hypotension (9%), dry mouth (8%), dizziness postural (5%), and bradycardia (5%).

A greater mean decrease from baseline in pulse rate, systolic and diastolic blood pressure (BP) in SPD503 treatment group was seen at the end of 13 weeks compared to placebo. The lowest point of pulse rate, systolic BP and diastolic BP tended to occur around treatment Week 3 and the values tended to return back to Baseline at the post-dose taper visits. Subjects receiving SPD503 had 3.7 bpm mean decrease from Baseline in supine pulse compared with a 1.0 bpm mean increase in subjects receiving placebo. SPD503 treatment was associated with 1.6 mmHg, and 1.3 mmHg mean decrease from Baseline in supine systolic BP and diastolic BP compared with a 0.5 mmHg and 0.1 mmHg mean increase in subjects receiving placebo. There was a greater mean decrease in standing systolic BP (-4.4 mmHg) and diastolic BP (-2.9 mmHg) in SPD503 treatment groups.

There were no clinically meaningful ECG changes associated with SPD503 treatment in Study SPD503-312.

Study SPD503-316

A total of 337 subjects were in the Safety Population: 111 in placebo; 114 in SPD503 and 112 in Strattera group in Study SPD503-316. The majority of subjects remained in the study >77 days. The mean optimal dose for the SPD503 group was 3.6mg, with over half of the subjects optimized at 3mg (28.8%) or 4mg (30.8%). The mean weight-adjusted optimal dose was 0.090mg/kg, with most subjects optimized at 0.05-0.08mg/kg (35.6%) or 0.09-0.12mg/kg (44.2%).

No death was reported during the conduct of Study SPD503-316. One subject receiving SPD503 experienced a SEA of syncope, which was a labeled AE.

Nine subjects (7.9%) receiving SPD503, 5 subjects (4.5%) receiving Strattera and 1 subject (0.9%) receiving placebo experienced TEAE(s) that led to discontinuation. No subjects discontinued due to an unlabeled AE.

The AE profile among SPD503 subjects were consistent with the know safety profile of the drug. Somnolence occurred in 16 (14.4%) subjects in the placebo group and 50 (43.9%) subjects in the SPD503 group. Somnolence is the only AE that met the most common adverse event criteria—that occurred $\geq 5\%$ and at least twice placebo rate. There were no clinically meaningful differences in the occurrence of TEAEs among children (6-12 years) and adolescents (13-17 years).

A greater mean decrease in pulse rate, systolic and diastolic blood pressure (BP) in SPD503 treatment group from baseline was seen at the endpoint compared to placebo. The magnitude of decrease in SPD503 group in pulse rate (-3.7 bpm), systolic (-1.6mmHg supine, -4.4mmHg standing) and diastolic blood (-1.3mmHg supine, -2.9mmHg standing) pressure at the endpoint were very similar to that seen in Study SPD503-312 and was consistent with our previous findings.

In summary, no new safety signals for SPD503 were evident in Studies SPD503-312, or SPD503-316. The AEs associated with SPD503 were consistent with the well-established SPD503 safety profile. The majority of TEAEs were mild or moderate, resolved prior to the end of the study, did not impact dosing or continuation in the study.

5. OPDP

The Office of Prescription Drug Promotion (OPDP) conducted review of the sponsor proposed labels and made a few recommendations that have been incorporated in the final product labeling.

6. OSI Inspection

The Office of Scientific Investigations (OSI) inspected selected data from 2 clinical study sites: Linda S. Harper, MD (Site 016, 18 subjects randomized), and John M. Turnbow, MD (Site 03, 20 subjects randomized). The OSI inspection did not find any major deficiencies and a Form FDA 483 was not issued. Overall, the study conduct appeared adequate, including informed consent, AE reporting, and drug accountability. IRB oversight and sponsor monitoring appeared acceptable. Source records were well organized and appeared complete. All audited endpoint data were verifiable among source records, CRFs, and NDA data listings. The OSI reviewer, John Lee, M.D., concluded that data from these sites are reliable for further agency review.

7. Labeling

Several revisions of physician labeling had been recommended by the review division, OCP team, OPDP, and MPHS. We are still in the process negotiating the labeling with the sponsor. The final agreed upon labeling will be attached to the action letter when this NDA is taken action.

8. Pediatric Plan

Study SPD503-312 was conducted to satisfy a post marketing commitment (PMC 1538-2) and a written request issued on April 1, 2011. The pediatric review committee had reviewed this submission. In the meeting on 10/22/2014, the committee concluded that the sponsor fulfilled the PMC requirement. The pediatric exclusivity board also reviewed the submission and felt that sponsor satisfied the written request requirement. An additional marketing exclusivity will be granted. No additional pediatric studies will be required.

9. Post Marketing Commitments or Requirements

No post marketing commitments are deemed necessary.

10. Risk Minimization Action Plan

No Risk Minimization Action Plan deemed necessary for this submission.

11. Conclusion and Recommendation

I agree with Dr. Sellers and Parfionovas's conclusion that that Study SPD503-312 and -316 have demonstrated that SPD503 was statistically significantly superior to placebo (p-value < 0.001 for both studies) in reducing the symptoms of ADHD measured by the mean change from baseline to endpoint in the ADHD-RS-IV total score in pediatric patients 6 to 17 years of age. There is no new safety signals identified in this supplement NDA review. The study conduct appeared adequate. I recommend that the division take an approval action on this submission. I also agree that Study SPD503-312 fulfilled the PMR (PMC 1538-2) and WR requirements.

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/s/

JING ZHANG
11/03/2014