Clinical Pharmacology Review

NDA:	022037
Generic Name:	Guanfacine
Trade Name:	INTUNIV©
Strength and Dosage Form:	1, 2, 3, 4 mg, extended release tablets for oral use
Indication:	ADHD
Sponsor:	Shire
Submission Type:	Efficacy Supplements (S#10 and S#11)
Priority Classification:	S#10 = Priority Review and S#11 = Standard Review
Submission Date:	May 19th, 2014 (for both S#10 and S#11)
PDUFA Dates:	Nov 19th, 2014 (for S#10) Mar 19th, 2015 (for S#11)
OCP Division:	DCP1
OND Division:	DPP
Reviewer:	Praveen Balimane, Ph.D.
Team Leader:	Hao Zhu, Ph.D.

Executive Summary

Shire has submitted two efficacy supplements (S#10 and S#11) on May 19th, 2014 for INTUNIV under NDA 022037. INTUNIV had been approved for ADHD in children and adolescents (6-17 years) on Sep 2nd, 2009. Efficacy supplement #10 is submitted to fulfill PMR-1538-2 (to demonstrate efficacy specifically in 13-17 yr adolescent group) and Written Request sent by Division on Apr 1st, 2011 and is supported by 2 short-term studies SPD503-312 and SPD503-316. Supplement #10 was designated a priority review with a goal date of Nov 19th, 2014. Efficacy supplement #11 is submitted to fulfill PMR-1538-1 (to demonstrate long-term efficacy and safety in pediatric subjects aged 6-17 yr) and is supported by 1 long-term maintenance study. Supplement #11 was designated a standard review with a goal date of Mar 19th, 2015. The two supplements (S#10 and S#11) were submitted by the sponsor intending to obtain the following labelling claims (1) safety and efficacy of INTUNIV in children and adolescents and (2) long-term maintenance dosing of INTINUV in children and adolescents with specific changes to section 2 (weight-based dosing up to 7 mg/day in adolescents), section 6 (relevant safety findings in children and adolescents) and section 14 (description of relevant clinical trials)

Listed below are the main study reports included in the two supplements:

Efficacy supplement #10

- Study SPD503-312 (intended to satisfy PMR 1538-2 and the pediatric written request) was a Phase 3, double-blind, randomized, multicenter, placebo-controlled study conducted to evaluate the efficacy, safety, and tolerability of SPD503 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. Subjects received SPD503 during a 7-week, dose-optimization period; followed by a 6- week, dose-maintenance period; a 2-week dose tapering period; and a 1-week, safety follow-up visit. This study was conducted in the US.

- Study SPD503-316 (additional short-term data in children and adolescents) was a Phase 3, double-blind, randomized, multicenter, placebo- and active-reference study conducted to evaluate the safety and efficacy of SPD503 in children and adolescents with a diagnosis of ADHD when given doses up to 7mg per day (dependent on age) using a flexible dose-optimization design. Subjects received the investigational product during a 4-week (children 6-12 years old) or 7-week (adolescents aged 13-17 years old) dose-optimization period followed by a 6-week dose-maintenance period, a 2-week dose tapering period, and a 1-week safety follow-up.

Efficacy supplement #11

- Study SPD503-315 (intended to satisfy PMR 1538-1) was a Phase 3, double-blind, placebo controlled, multicenter, randomized-withdrawal study conducted to evaluate the long-term maintenance of efficacy and safety of SPD503 in pediatric subjects aged 6-17 years with a diagnosis of ADHD. The study consisted of a 7-week, open-label, dose-optimization period; a 6-week, open-label, dose-maintenance period with optimized SPD503; a 26-week, double-blind, randomized-withdrawal phase; a 2-week post-treatment, double-blind dose-tapering period; and a 1-week safety follow-up. This study was conducted at centers in North America and Europe.

The Office of Clinical Pharmacology (OCP) believes that the two sNDAs are acceptable from clinical pharmacology point of view. OCP's 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 7 mg/day. Our analyses found that the new higher dose of 7 mg/day in adolescents is acceptable.

Clinical Pharmacology Summary

INTUNIV® (Guanfacine) is a central aplha2A-adrenergic agonist and is available as an extended release oral tablet. It is approved for treatment of ADHD at recommended dose of 1 to 4 mg once daily.

Clinical Pharmacology review focused on assessing the suitability of new higher dose of 7 mg/day in adolescents contrasted with currently approved top dose of 4 mg in adolescents. The higher 7 mg /day dose level was found to be acceptable for adolescents based on the following rationales.

Rationale #1:

INTUNIV's pharmacokinetics is known to be weight-based with higher exposures in children (6-12 yr) compared to adolescents (13-17 yr). Based on the weight difference, given the same dose, exposures in children were roughly 40% higher than that in adolescents (Table 1)

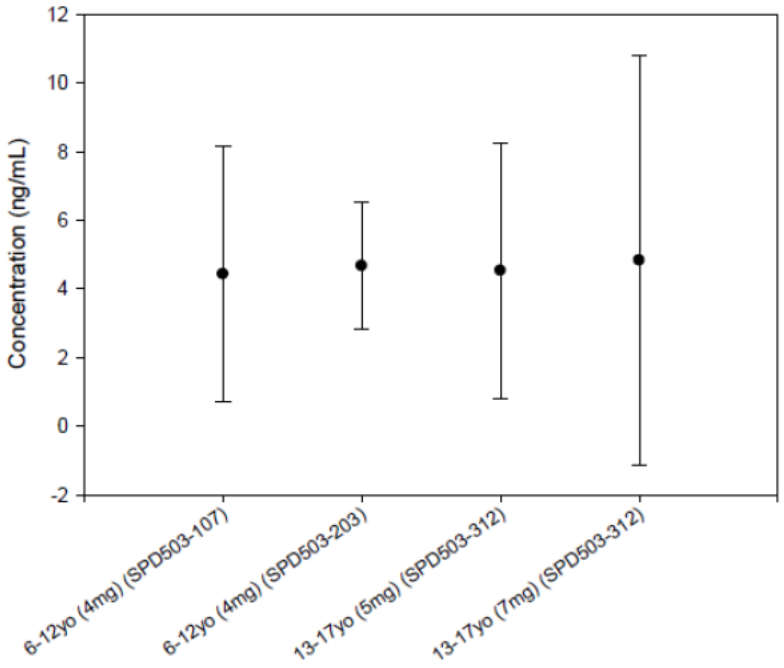
Table 1: Comparison of exposure between children (6-12 yr) and adolescents (13-17 yr)

Dose	Exposure in 6-12 yr		Exposure in 13-17 yr	
	Cmax (ng/mL)	AUC (ng*h/mL)	Cmax (ng/mL)	AUC (ng*h/mL)
4 mg	10	162	7	116

Since INTUNIV's pharmacokinetics is known to be dose-proportional, the exposure in adolescents at 7 mg dose is expected to be similar to the exposure in children at the currently approved 4 mg dose. This was confirmed by Population PK data which demonstrated that the "trough" levels were similar in adolescents (13-17 yr) at 7 mg dose level (in recent short-term efficacy study SPD502-312) compared to children (6-12 yr) at 4 mg dose level (in past 2 studies SPD503-107 and SPD503-203).

Fig 1 demonstrates that trough concentrations were similar in children (at 4 mg) compared to adolescents (at 7 mg) suggesting that exposures are similar for the two groups even though adolescents are dosed a higher dose (7 mg). There was only limited data available for this comparison since study SPD503-312 was not specified to obtain trough samples.

Figure 1 Comparison of Guanfacine Steady State Trough Exposures



Rationale #2:

In both studies (SPD503-315 and SPD503-316, where flexible dosing was allowed with children getting a max dose of 4 mg and adolescents getting a max dose of 7 mg), 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. Table 2 demonstrates that similar percentage of subjects are escalated to higher doses in both age groups, providing confirmatory evidence that higher doses up to 7 mg are well-tolerated in adolescents (based on their weight).

Table 2: Percentage of subjects escalated to higher dose

Study #	% of children at 4 mg	% of adolescents at 5-7 mg
SPD503-315	44%	45%
SPD503-316	33%	33%

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/s/

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10/27/2014

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10/27/2014