5.06 GUANFACINE, Tablet containing guanfacine hydrochloride 1 mg, 2 mg, 3 mg and 4 mg, Intuniv®, Shire Australia Pty Limited

1 Purpose of Application

1.1 Authority Required listing for guanfacine for treatment of attention deficit hyperactivity disorder (ADHD) in those who are (i) contraindicated to stimulants (used as monotherapy), (ii) intolerant to stimulants (used as monotherapy) and (iii) failing to achieve an adequate response to stimulants (used as monotherapy or as adjunctive therapy with stimulants).

1.2 Table 1 presents the key components of the clinical issue addressed by the submission.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Attention deficit hyperactivity disorder (ADHD) in those who are (i) contraindicated to stimulants, (ii) intolerant to stimulants or (iii) failing to achieve an adequate response to stimulants. Aged 6-18 years inclusive.
Intervention	Guanfacine to be used as monotherapy in all three populations listed above and as adjunctive therapy to stimulants in those failing to achieve an adequate response to stimulants
Comparator	Atomoxetine for those who are (i) contraindicated or (ii) intolerant to stimulants; and Placebo for no treatment for those who are (iii) failing to achieve an adequate response to stimulants. Clonidine was nominated as a secondary comparator for this population.
Outcomes	Change in ADHD-RS-IV total score from baseline to endpoint Responder rates (differentially defined in the trials as a ADHD-RS-IV total score reduction of ≥30% and CGI-I ≤2 or ADHD-RS-IV total score reduction of ≥25%) Symptomatic remission (defined as ADHD-RS-IV total score ≤18) Syndromal remission (ADHD-RS-IV total score ≤18 AND CGI-S ≤2)
Clinical claim	<u>Contraindicated/intolerant to stimulants</u> The submission described guanfacine as superior in terms of comparative effectiveness and as "having a trend towards [comparative] inferior safety" over atomoxetine in patients who are "contraindicated to stimulant therapy or are switching to guanfacine monotherapy due to poor tolerability". <u>Failing to achieve an adequate response to stimulants</u> The submission described guanfacine in combination with stimulant therapy as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo in combination with stimulant therapy in patients who "intend to support the use of guanfacine as add-on therapy in patients who have an unsatisfactory response on optimal stimulant therapy".

ADHD-RS-IV= attention deficit hyperactivity disorder rating scale IV; CGI-I=Clinical Global Impression - Improvement; CGI-S=Clinical Global Impression - Severity of Illness. Source: compiled during the evaluation

1.3 The claim of superior comparative effectiveness of guanfacine versus atomoxetine and guanfacine + long-acting stimulants versus placebo + long-acting stimulants requires consideration as although a statistically significant difference in the change in total ADHD-RS-IV scores were observed:

- The comparison of guanfacine and atomoxetine was a post-hoc comparison of the trial; and
- No minimally clinically important differences (MCIDs) have been validated for between treatment changes in ADHD-RS-IV total scores (ie the minimum difference between two treatments that can be considered clinically relevant). The ESC noted, however, that the submission adopted an assumption of non-inferiority in taking a cost-minimisation approach to atomoxetine for patients contraindicated or intolerant to stimulants.

For more detail on PBAC's view, see section 7 "PBAC outcome"

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
GUANFACINE HYDROCHLORIDE Extended release tablets (1mg, 2mg, 3mg, 4mg)	28	5	$[redacted][a]	INTUNIV®	Shire Australia Pty Ltd

Category / Program	General Schedule
PBS indication	Attention deficit hyperactivity disorder
Restriction	Authority required
Treatment criteria	The condition must be or have been diagnosed by a paediatrician or psychiatrist according to the DSM-5 criteria
Clinical criteria	Patient must have a contraindication to dexamphetamine, methylphenidate or lisdexamfetamine as specified in TGA-approved product information; OR Patient must have a comorbid mood disorder that has developed or worsened as a result of dexamphetamine, methylphenidate or lisdexamfetamine treatment and is of a severity necessitating treatment withdrawal; OR Patient must be at an unacceptable medical risk of a severity necessitating permanent stimulant treatment withdrawal if given a stimulant treatment with another agent; OR Patient must have experienced adverse reactions of a severity necessitating permanent treatment withdrawal following treatment with dexamphetamine, methylphenidate and lisdexamfetamine (not simultaneously); OR Patient must have failed to achieve a satisfactory response to optimised stimulant therapy.
Population criteria	Patient must be between the ages of 6 and 18 years inclusive

[a] requested published price. The submission is requesting a Special Pricing Arrangement (SPA) with an effective DPMQ of $[redacted].

2.1 The requested basis for listing was cost-minimisation compared with atomoxetine among those contraindicated/intolerant to stimulants and cost-effectiveness when used in combination with long-acting stimulants compared to placebo in combination

with long-acting stimulants for patients who have failed to achieve a satisfactory response.

2.2 Guanfacine is taken orally, once daily. Patients initiate on 1mg/day and increase in 1mg increments weekly to a maximum dose of 4mg/kg in those aged 6-12 years and to a maximum dose of 7mg/day in those aged 13-17 years. For adjunctive therapy the maximum dose is 4mg/day. Discontinuation of guanfacine requires dose tapering to avoid adverse events.

2.3 The inclusion of patients aged 18 in the requested listing is not supported by the clinical data submitted and is inconsistent with the TGA indication being sought, which includes children and adolescents aged 6-17 years. The ESC noted the PSCR (p4) states that in estimating the potential patient population for the financial implications, "it is proposed that the eligible patient population is for 6-17 years inclusive, to align with the TGA indication".

2.4 The submission requested a Special Pricing Arrangement (SPA) with a list price of $[redacted] and an effective price of $[redacted]. The Sponsor has indicated that listing would not proceed without an SPA.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

3.1 TGA status: The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluator's Report, the Delegate's Overview and the ACM advice were available.

3.2 Guanfacine has not previously been considered by the PBAC.

4 Population and disease

4.1 Attention deficit hyperactivity disorder (ADHD) is a heterogeneous behavioural syndrome characterised by the core symptoms of hyperactivity, impulsivity and inattention.

4.2 The submission proposed that guanfacine be listed for patients with ADHD in those who are (i) contraindicated to stimulants, (ii) intolerant of stimulants or (iii) who have failed to achieve an adequate response to stimulants. For those contraindicated and intolerant to stimulants, guanfacine is proposed to be an alternative to atomoxetine and in those failing to achieve an adequate response to stimulants, that guanfacine replace or be used as add-on therapy to stimulants. However, the ESC noted that the clinical evidence presented to support the cost-effectiveness claim for patients with an inadequate response was the use of guanfacine as an add-on and not a replacement of stimulants.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

5.1 Atomoxetine for those contraindicated or intolerant to stimulants. The PBAC agreed this was the appropriate comparator.

5.2 Placebo (as a proxy for no treatment) was nominated as the primary comparator, and clonidine as a secondary comparator for those who are failing to achieve and adequate response to stimulants. Placebo for no treatment would be the relevant comparator in instances where all stimulants have been trialled and failed, otherwise stimulants would be a relevant comparator. Clonidine is not PBS-listed for ADHD and its safety, effectiveness and cost-effectiveness are therefore unknown, thus the evidence provided in the submission for this comparison was not considered by the evaluation. The ESC acknowledged that clonidine is the closest analogue to guanfacine, however, considered that clonidine is not a relevant secondary comparator given its off-label use is in a population for which it is formally not recommended. The PBAC agreed with the ESC and considered that clonidine is not a relevant secondary comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described the heterogeneous causal nature of ADHD, clinical presentations of ADHD, and how patients may respond to therapies. The clinician described generally good response rates to stimulant therapy, but described two patient groups who would benefit from access to guanfacine: (1) as an alternative to atomoxetine with a novel mechanism of action in patients who are contraindicated or intolerant to stimulants, and (2) as a new adjunctive therapy option for patients who have a partial response to stimulant therapy, as atomoxetine cannot be used for that purpose.

6.2 The clinician described the difference between response and remission in ADHD using the ADHD-RS-IV scale, and that while a response may represent an improvement in ADHD, that remission was the primary objective of treatment as it provided the best functional and quality of life outcomes for patients. The clinician stated that the primary population for guanfacine would be for patients who are contraindicated or intolerant to stimulants, which represents up to approximately [redacted]% of the ADHD population. The clinician stated that use of guanfacine as an adjunctive therapy to stimulants would be for a small population ([redacted]%-[redacted]% of patients not achieving optimal response ie remission), but would help these patients achieve remission, and that adjunctive therapy may provide combination effects with stimulants to address different types of symptoms.

6.3 The clinician stated that the requested listing and TGA indication did not include patients 18 years and over as there is no body of evidence to support its use in these patients, but commented that from a clinician's perspective it is difficult to cease treatment in patients who are benefiting from treatment, or to not be able to commence adult patients on therapy.

Consumer comments

6.4 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.5 The submission was based on:

- one head-to-head randomised trial comparing guanfacine to placebo and atomoxetine (Trial 316). The primary analysis for Trial 316 was a comparison of guanfacine and placebo; the comparison of guanfacine and atomoxetine was post-hoc; and
- one head-to-head trial comparing guanfacine and placebo as an adjunctive to stimulant therapy in patients with a suboptimal response to long-acting psychostimulant (ADHD-RS-IV score of ≥24) and having a need for additional treatment in the opinion of the Investigator (Trial 313).

6.6 The submission included an additional six trials (Trials 206, 301, 304, 307, 312 and 314) as supplementary evidence.

6.7 The economic analyses presented by the submission rely only on Trials 316 and 313.

6.8 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial	Protocol title / Publication title	Publication citation
Direct randomised trials		
Guanfacine versus atomoxetine (and placebo)		
Trial 316	A Phase 3, Randomised, Double-blind, Multicentre, Parallel-Group, Placebo- and Active-reference, Dose-optimisation Efficacy and Safety Study of Extended-release Guanfacine Hydrochloride in Children and Adolescents Ages 6-17 Years With Attention-Deficit/Hyperactivity Disorder	15 October 2013
	Hervas A, Huss M, Johnson M, et al. Efficacy and safety of extended-release guanfacine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder: A randomized, controlled, Phase III trial.	Eur. Neuropsychopharmacol. 2014; 24(12): 1861-1872
	Hervás A, Johnson M, McNicholas F, et al. Clinical global impressions-improvement scores by visit in a European, randomized, double-blind, placebo and active-controlled clinical trial of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder.	Eur. Child Adolesc. Psychiatry 2015; 24(1): S138
	Huss M, Johnson M, McNicholas F, et al. Attention-deficit/hyperactivity disorder rating scale IV subscale analysis by visit in a European, phase 3, randomized, double-blind clinical trial of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity deficit.	Eur. Child Adolesc. Psychiatry 2015; 24(1): S133-S134

Trial	Protocol title / Publication title	Publication citation
Guanfacine + stimulant versus placebo + stimulant		
Trial 313	A Phase 3, Double-blind, Randomized, Placebo-controlled, Multicenter, Dose-optimization Study Evaluating the Efficacy and Safety of SPD503 in Combination With Psychostimulants in Children and Adolescents Aged 6-17 Years With a Diagnosis of Attention-deficit Hyperactivity Disorder (ADHD)	30 March 2010
	Wilens TE, Bukstein O, Brams M, et al. A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder.	J. Am. Acad. Child Adolesc. Psychiatry 2012; 51(1): 74-85
	Findling RL, McBurnett K, White C & Youcha S. Guanfacine extended release adjunctive to a psychostimulant in the treatment of comorbid oppositional symptoms in children and adolescents with attention-deficit/hyperactivity disorder.	J. Child Adolesc. Psychopharmacol. 2014; 24(5): 245-252
	Cutler AJ, Brams M, Bukstein O, et al. Response/remission with guanfacine extended-release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder.	J. Am. Acad. Child Adolesc. Psychiatry 2014; 53(10): 1092-1101
Guanfacine versus placebo		
Trial 206	A phase II study to assess the safety, tolerability and efficacy of SPD503 administered to children and adolescents aged 6-17 years with attention-deficit/hyperactivity disorder (ADHD)	24 April 2006
	Kollins SH, López FA, Vince BD, et al. Psychomotor functioning and alertness with guanfacine extended release in subjects with attention-deficit/hyperactivity disorder.	J. Child Adolesc. Psychopharmacol. 2011, 21(2): 111-120.
Trial 301	A phase III, randomised, multi-center, double-blind, parallel-group, placebo controlled safety and efficacy study of SPD503 in children and adolescents aged 6-17 with attention deficit hyperactivity disorder (ADHD)	16 March 2006
	Biederman J, Melmed RD, Patel A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder.	Pediatr. 2008, 121(1): e73-e84.
Trial 304	A phase II study to assess the safety, tolerability and efficacy of SPD503 administered to children and adolescents aged 6-17 with attention-deficit/hyperactivity disorder (ADHD)	2 May 2006
	Sallee FR, McGough J, Wigal T, et al. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: A placebo-controlled trial.	J. Am. Acad. Child Adolesc. Psychiatry 2009, 48(2): 155-165
Trial 307	A double-blind, randomized, multi-center, flexible dose study evaluating the efficacy and safety of SPD503 in children aged 6-12 with symptoms of oppositionality and a diagnosis of attention-deficit/hyperactivity disorder	
	Connor D, Kollins S, Findling R, et al. Effects of guanfacine extended release in children aged 6 to 12 years with oppositional symptoms and a diagnosis of attention-deficit/ hyperactivity disorder.	Biol. Psychiatry 2010, 67(9): 217S.
	Connor DF, Findling RL, Kollins SH, et al. Effects of guanfacine extended release on oppositional symptoms in children aged 612 years with attention-deficit hyperactivity disorder and oppositional symptoms: A randomized, double-blind, placebo-controlled trial.	CNS Drugs 2010, 24(9): 755-768.
	Lopez FA, Lyne A & Youcha S. Efficacy of guanfacine extended release in children with oppositional symptoms and attention-deficit/hyperactivity disorder: A responder analysis.	J. Pharm. Pract. 2010, 23(2): 155-156.
	Sallee F, Spencer T, Connor D, et al. 2009. Effects of guanfacine extended release on secondary measures in children with attention- deficit/hyperactivity disorder and oppositional symptoms.	Biol. Psychiatry 2009, 65(8): 149S.
	Youcha S, Sallee FR, Connor DF, et al. Effects of guanfacine extended release on individual oppositional symptoms in children with attention-deficit/hyperactivity disorder and the presence of oppositional symptoms.	J. Pharm. Pract. 2010, 23(2): 155.
	Youcha S, Connor DF, Sallee FR & Lyne A. Changes in parental stress with	J. Pharm. Pract. 2010,

Trial	Protocol title / Publication title	Publication citation
	guanfacine extended release in children with attention-deficit/hyperactivity disorder and oppositional symptoms.	23(2): 153.
Trial 312	A phase 3, double-blind, randomized, multi-center, placebo-controlled, dose-optimization study evaluating the safety, efficacy, and tolerability of once-daily dosing with extended-release guanfacine hydrochloride in adolescents aged 13-17 years diagnosed with attention-deficit/hyperactivity disorder (ADHD)	3 October 2013
	Wilens TE, Robertson B, Sikirica V, et al. A Randomized, Placebo-Controlled Trial of Guanfacine Extended Release in Adolescents With Attention-Deficit/Hyperactivity Disorder.	J. Am. Acad. Child Adolesc. Psychiatry 2015, 54(11): 916-925.
	Wilens TE, Harper L, Young JL, et al. 2015. Clinical response and symptomatic remission in adolescents with Attention-Deficit/Hyperactivity Disorder receiving guanfacine extended release in a phase 3 study.	ADHD Attention Deficit and Hyperactivity Disorders, 7S98.
	Cutler A, Harper L, Young J, et al. Guanfacine extended release: Daytime sleepiness outcomes from a phase 3 clinical study in adolescents with attention-deficit/hyperactivity disorder.	Eur. Neuropsychopharmacol. 2015, 25S648-S649.
Trial 314	A phase 3, double-blind, randomized, multi-center, placebo-controlled, dose-optimization study evaluating the tolerability and efficacy of AM and PM once-daily dosing with extended-release guanfacine hydrochloride in children aged 6-12 years with a diagnosis of attention-deficit/hyperactivity disorder	28 January 2011
	Newcorn JH, Stein MA, Childress AC, et al. Randomized, double-blind trial of guanfacine extended release in children with attention-deficit/hyperactivity disorder: Morning or evening administration.	J. Am. Acad. Child Adolesc. Psychiatry 2013, 52(9): 921-930.
	Young J, Rugino T, Dammerman R, et al. Efficacy of guanfacine extended release assessed during the morning, afternoon, and evening using a modified conners' parent rating scale-revised: Short form.	J. Child Adolesc. Psychopharmacol. 2014, 24(8): 435-441
	Stein MA, Sikirica V, Weiss MD, et al. Does Guanfacine Extended Release Impact Functional Impairment in Children with Attention-Deficit/Hyperactivity Disorder? Results from a Randomized Controlled Trial.	CNS Drugs 2015, 29(11): 953-962.

Source: Table B-2 (pp 45-47)

6.9 The key features of the direct randomised trials are summarised in Table 3. Patients in Trial 313 were on stable doses of long-acting stimulants (some of which are not available in Australia), however the majority of patients were co-administered with stimulants available on the PBS - Concerta® (45.3%), lisdexamfetamine (29.5%) or Ritalin LA® (0.4%).

Table 3: Key features of the included evidence

Trial	N[a]	Design/duration of DB evaluation	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Guanfacine versus atomoxetine (and placebo)						
Trial 316	338	R, DB 10 weeks (6-12) 13 weeks (13-17)	Low	ADHD, ADHD-RS-IV ≥32, CGI-S ≥3, excluded those who were well controlled on their current (ADHD) medication, with acceptable tolerability, and the parent/caregiver did not object to the current medication, aged 6-17 years	• Change in ADHD-RS-IV total score[c] • Proportion responders (ADHD-RS-IV reduction ≥30% and CGI-I ≤2) • Proportion in symptomatic remission (ADHD-RS-IV total score ≤18) and syndromal remission (ADHD-RS-IV total score ≤18 AND CGI-S ≤2) • HUI 2/3	Not used[b]
Guanfacine + stimulant versus placebo + stimulant						
Trial 313	461	R, DB 8 weeks	Low	ADHD, ADHD-RS-IV ≥24, CGI-S ≥3, with a suboptimal response to long-acting psychostimulant and had a need for additional treatment in the opinion of the Investigator, aged 6-17 years	• Change in ADHD-RS-IV total score[c] • Proportion responders (ADHD-RS-IV reduction ≥25%) • Proportion in symptomatic remission (ADHD-RS-IV total score ≤18) and syndromal remission (ADHD-RS-IV total score ≤18 AND CGI-S ≤2)	Yes Symptomatic remission used in the base case and syndromal remission and responder used in sensitivity analyses
Guanfacine versus placebo						
Trial 206	182	R, DB 6 weeks	Low	ADHD, ADHD-RS-IV ≥24, CGI-S ≥4 aged 6-17 years	• Change in ADHD-RS-IV total score[c] [all trials] • Proportion responders (ADHD-RS-IV reduction ≥30% and CGI-I ≤2 [Trials 307, 312, 314] OR ADHD-RS-IV reduction ≥25% [Trial 304]) • Proportion in symptomatic remission (ADHD-RS-IV total score ≤18 [Trials 312 and 314]) and syndromal remission (ADHD-RS-IV total score ≤18 AND CGI-S ≤2 [Trial 314]) • HUI 2/3 [Trial 314]	Not used
Trial 301	345	R, DB 5 weeks	Low	ADHD, aged 6-17 years		Not used
Trial 304	324	R, DB 6 weeks	Low	ADHD, ADHD-RS-IV ≥24, aged 6-17 years		Not used
Trial 307	217	R, DB 8 weeks	Low	ADHD, ADHD-RS-IV ≥24, CGI-S ≥4 aged 6-12 years		Not used
Trial 312	314	R, DB 13 weeks	Low	ADHD, ADHD-RS-IV ≥32, CGI-S ≥4, aged 13-17 years		Not used
Trial 314	340	R, DB 8 weeks	Low	ADHD, ADHD-RS-IV ≥28, CGI-S ≥4, aged 6-12 years		Not used

ADHD=attention deficit hyperactivity disorder; ADHD-RS-IV=attention deficit hyperactivity disorder rating scale IV; CGI-I=Clinical Global Impression - Improvement; CGI-S=Clinical Global Impression - Severity of Illness; DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.

[a] randomised
[b] not used in modelled economic evaluation, but used in a cost-minimisation analysis versus atomoxetine
[c] full analysis set (FAS), defined as 'randomised subjects who took at least 1 dose of investigational product', to analyse efficacy and safety outcomes, used LOCF for missing efficacy data.
Source: compiled during the evaluation

Comparative effectiveness

6.10 Table 4 summarises the changes in ADHD-RS-IV total scores from baseline to endpoint in the trials.

Table 4: Mean change in ADHD-RS-IV scores

Trial	Week	N	Mean change (SD)	N	Mean change (SD)	Mean difference (95% CI)
		GXR		**ATX**		
Trial 316	10/13	112	-23.9 (12.41)	112	-18.6 (11.91)	**-5.30 (-8.49, -2.11)**
		GXR + LA stimulants		**PBO + LA stimulants**		
Trial 313	8	297	-20.7 (12.56)	152	-16.0 (11.77)	**-4.70 (-7.05, -2.35)**
		GXR		**PBO**		
Trial 316	10/13	112	-23.9 (12.41)	111	-15.0 (13.07)	**-8.90 (-12.25, -5.55)**
Trial 206	6	118	-18.0 (10.72)	57	-11.9 (13.12)	**-6.10 (-10.02, -2.18)**
Trial 301	5	81	-19.0 (13.71) – 4mg	78	-8.86 (12.90)	**-10.14 (-14.28, -6.00)**
Trial 304	6	63	-20.9 (11.89) – 4mg	63	-12.2 (12.96)	**-8.70 (-13.04, -4.36)**
Trial 307	8	130	-23.8 (14.43)	75	-11.4 (12.65)	**-12.40 (-16.19, -8.61)**
Trial 312	13	109	-25.7 (10.09)	106	-19.5 (12.63)	**-6.20 (-9.26, -3.14)**
Trial 314	8	216	-20.0 (12.97)	110	-11.0 (12.93)	**-9.00 (-11.97, -6.03)**
Pooled (all trials) Chi-square for heterogeneity: P=0.21; I^2 statistic = 29%						[redacted]
Pooled (Trials 316, 206, 307, 312, 314 – dose optimised trials) Chi-square for heterogeneity: P=0.10; I^2 statistic=49%						[redacted]
Pooled (Trials 316, 307, 312, 314 – maximum dose optimised trials) Chi-square for heterogeneity: P=0.10; I^2 statistic=52%						[redacted]

Source: Table B-17, p102; Table B-23, p108; and Table B-29, p116 of the submission
Bold typography indicates statistically significant differences

6.11 A statistically significant reduction in ADHD-RS-IV scores was demonstrated in both the comparison of guanfacine versus atomoxetine (Trial316) and guanfacine ± long-acting stimulants versus placebo ± long-acting stimulants (Trial 313). The 95% CI for the mean difference in ADHD-RS-IV between treatment groups within comparisons of guanfacine and atomoxetine (Trial 316) and guanfacine + long-acting stimulants versus placebo + long-acting simulants (Trial 313) include both the 'within treatment' and 'between treatment' MCIDs threshold ADHD-RS-IV score changes from Zhang et al (2005) of between 9.6 and 11.4, and 5.2 to 7.7 respectively. Given this, and the fact there are no other validated MCIDs for the ADHD-RS-IV in children and adolescents, there is no robust evidence to support guanfacine and guanfacine + long-acting stimulants as offering a clinically significant improvement compared to atomoxetine and placebo + long-acting stimulants, respectively. The ESC noted the mean difference in both trials did not reach the pre-specified mean difference of 6.6 (as specified in Zhang et al 2005), and considered that the results were unlikely to indicate a MCID for guanfacine and atomoxetine.

6.12 For the comparison of guanfacine and placebo, the interpretation of clinical significance is dependent on the MCID that is considered most acceptable. As the 'within treatment' MCID reported by Zhang et al (2005) has been validated against the CGI-I scale, there could be an argument that a clinically significant difference remains constant regardless of the comparison. The 95% CIs in the comparison of guanfacine and placebo do not exceed any of these MCIDs, thus the clinical significance of the changes in ADHD-RS-IV total scores required consideration. The ESC noted ADHD-RS-IV score changes between 25-30% have been validated as meaningful (Goodman et al 2010), and that these percentage changes have been used in the trials to classify participants as responders and non-responders.

6.13 Table 5 summarises the proportion of patients achieving 'responder' status in the trials.

Table 5: Proportion classified as a responder in the trials

Trial	n/N (%)	n/N (%)	RR (95% CI)	RD (95% CI)	NNT (95% CI)
	GXR	**ATX**			
Trial 316[a]	72/112 (64.3)	62/112 (55.4)	1.16 (0.94, 1.44)	0.09 (-0.04, 0.22)	NA
	GXR+LA stimulants	**PBO+LA stimulants**			
Trial 313[b]	241/297 (81.1)	106/152 (69.7)	**1.16 (1.03, 1.31)**	**0.11 (0.03, 0.20)**	**9 (5, 33)**
	GXR	**PBO**			
Trial 316[a]	72/112 (64.3)	47/111 (42.3)	**1.52 (1.17, 1.96)**	**0.22 (0.09, 0.35)**	**4 (3 11)**
Trial 304[b]	51/63 (81.0) – 4mg 182/243 (74.9) - all	36/63 (57.1)	**1.42 (1.11, 1.81)** **2.24 (1.26, 3.99)**	**0.24 (0.08, 0.39)** **0.18 (0.04, 0.31)**	**4 (3, 13)** **5 (3, 25)**
Trial 307[a]	90/130 (69.2)	23/74 (31.1)	**2.23 (1.56, 3.19)**	**0.38 (0.25, 0.51)**	**3 (2, 4)**
Trial 312[a]	103/154 (66.9)	71/155 (45.8)	**1.46 (1.19, 1.79)**	**0.21 (0.10, 0.32)**	**5 (3, 10)**
Trial 314[a]	132/215 (61.4)	34/110 (30.9)	**1.99 (1.47, 2.68)**	**0.30 (0.20, 0.41)**	**3 (2, 5)**
Pooled (all trials), using 4mg GXR from Trial 304 Chi-square for heterogeneity:			**1.64 (1.39, 1.93)** P=0.10; I^2 statistic=48%	**0.27 (0.21, 0.33)** P=0.28 I^2 statistic=21%	**4 (3, 5)**
Pooled (all trials), using lumped (all) GXR from Trial 304 Chi-square for heterogeneity:			[redacted]	[redacted]	[redacted]
Pooled (Trials 316, 307, 312, 314 – dose optimised trials, all trials also had same definition of 'responder'[a]) Chi-square for heterogeneity:			[redacted]	[redacted]	[redacted]

Source: Table B-18, p102; Table B-24, p109 and Table B-30, p118 of the submission

[a] responder defined as a reduction of ≥30% in ADHD-RS-IV and CGI-I ≤2

[b] responder defined as a reduction of ≥25% in ADHD-RS-IV

RR=relative risk, RD=risk difference, NNT=number need to treat, CI=confidence interval

Bold typography indicates statistically significant differences

6.14 No statistically significant difference was observed between those treated with guanfacine or atomoxetine for the proportion of patients who were classified as responders (defined as a reduction of ≥30% in ADHD-RS-IV and CGI-I ≤2) in Trial 316. A statistically significantly greater proportion of patients were classified as responders in the comparison of guanfacine ± long-acting stimulants versus placebo ± long-acting stimulants; defined as ≥30% change in ADHD-RS-IV AND CGI-I ≤2 in Trials 316, 307, 312, 314; or as ≥25% change in ADHD-RS-IV in Trials 313 and 304. Although Trial 313 had a lower level of ADHD total score reduction in the definition of responder, this

was measuring the additional level of response above suboptimal responses to concomitant stimulants and may be considered reasonable.

6.15 Table 6 summarises the proportion of patients achieving 'remission' status in the trials as defined by a score of ≤18.

Table 6: Proportion classified as being in 'remission' in the trials

Trial	n/N (%)	n/N (%)	RR (95% CI)	RD (95% CI)	NNT (95% CI)
Symptomatic remission (ADHD-RS-IV total score ≤18)					
	GXR	**ATX**			
Trial 316	57/112 (50.9)	38/112 (33.9)	**1.50 (1.09, 2.06)**	**0.17 (0.04, 0.30)**	**6 (3, 25)**
	GXR+LA stimulants	**PBO+LA stimulants**			
Trial 313	183/297 (61.6)	70/152 (46.1)	**1.34 (1.10, 1.62)**	**0.16 (0.06, 0.25)**	**6 (4, 17)**
	GXR	**PBO**			
Trial 316	57/112 (50.9)	31/111 (27.9)	**1.82 (1.28, 2.59)**	**0.23 (0.10, 0.35)**	**4 (3, 10)**
Trial 312	95/154 (61.7)	64/155 (41.3)	**1.49 (1.19, 1.87)**	**0.20 (0.09, 0.31)**	**5 (3, 11)**
Trial 314	101/216 (46.8)	20/110 (18.2)	**2.57 (1.69, 3.92)**	**0.29 (0.18, 0.38)**	**3 (3, 5)**
Pooled (all trials) Chi-square for heterogeneity:			[redacted]	[redacted]	[redacted]
Syndromal remission (ADHD-RS-IV total score ≤18 AND CGI-S ≤2)					
	GXR+LA stimulants	**PBO+LA stimulants**			
Trial 313	129/297 (43.4)	45/152 (29.6)	**1.47 (1.11, 1.94)**	**0.14 (0.05, 0.23)**	**7 (4, 20)**
	GXR	**PBO**			
Trial 314	63/216 (29.2)	12/110 (10.9)	**2.67 (1.51, 4.74)**	**0.18 (0.10, 0.27)**	**4 (3, 10)**

Bold typography indicates statistically significant differences
RR=relative risk, RD=risk difference, NNT=number need to treat, CI=confidence interval, NA = not applicable
Source: T able B-19, p103, Table B-25, p110 and Table B-31, p120 of the submission

6.16 A statistically significantly greater proportion of those treated with guanfacine ± long-acting stimulants achieved "symptomatic" or "syndromal" remission compared with those treated with atomoxetine or placebo ± long-acting stimulants. Unlike the "responder" analysis, this outcome does not take into consideration baseline ADHD-RS-IV scores, where those with higher baseline ADHD-RS-IV would presumably be less likely to reach these thresholds.

Comparative harms

6.17 Compared with atomoxetine; those treated with guanfacine were statistically significantly more likely to experience somnolence, diarrhoea and increased appetite, and less likely to experience a sedative event, vomiting, nausea and decreased appetite.

6.18 Compared with placebo + long-acting stimulants, those treated with guanfacine + long-acting stimulants were statistically significantly more likely to experience any treatment-emergent adverse event, somnolence, headache, sedative event, abdominal pain (upper) and fatigue.

6.19 Compared with placebo as monotherapy, those treated with guanfacine as monotherapy were statistically significantly more likely to experience any treatment emergent adverse event (TEAE), TEAEs related to drug, severe TEAE, withdrawal or

dose reduction due to TEAE, somnolence, headache, sedation, gastrointestinal disorders, abdominal pain (upper), dry mouth, fatigue and irritability.

Benefits and harms

6.20 Summaries of the comparative benefits and harms for guanfacine ± long-acting stimulants versus placebo ± long-acting stimulants, and for guanfacine versus atomoxetine are presented in Tables 7 and 8. Symptomatic remission was the outcome used in the base case of the modelled economic evaluation. The submission presented a cost-minimisation analysis versus atomoxetine.

Table 7: Summary of comparative benefits and harms for guanfacine and placebo*

Benefits							
Symptomatic remission (ADHD-RS-IV total score ≤18)							
Trial	**Guanfacine**	**Placebo**	**RR (95% CI)**	**Events/100 patients***		**RD (95% CI)**	
				Guanfacine	**Placebo**		
Trial 313 Used in combination with stimulants	183/297	70/152	**1.34 (1.10, 1.62)**	61.6	46.1	**0.16 (0.06, 0.25)**	
Responder (reduction in ADHD-RS-IV of ≥25% [Trials 313, 304] or ≥30% and CGI-I ≤2 [Trials 316, 307, 312, 314])							
Trial 313 Used in combination with stimulants	241/297	106/152	**1.16 (1.03, 1.31)**	81.1	69.7	**0.11 (0.03, 0.20)**	
Mean change in ADHD-RS-IV scores							
Trial	**Guanfacine**			**Placebo**			**Mean difference* (95% CI)**
	n	**Mean Δ**	**SD**	**n**	**Mean Δ**	**SD**	
Trial 313 Used in combination with stimulants	297	-20.7	12.56	152	-16.0	11.77	**-4.70 (-7.05, -2.35)**
Harms							
	Guanfacine	**Placebo**	**RR (95% CI)**	**Events/100 patients***		**RD (95% CI)**	
				Guanfacine	**Placebo**		
Abdominal pain (upper)							
Trial 313 Used in combination with stimulants	25/302	3/153	**4.22 (1.39, 13.04)**	8.3	2.0	**0.06 (0.02, 0.10)**	
Somnolence							
Trial 313 Used in combination with stimulants	41/302	7/153	**2.97 (1.40, 6.38)**	13.6	4.6	**0.09 (0.03, 0.14)**	

Abbreviations: PBO = placebo; RD = risk difference; RR = risk ratio
*Trial 313 duration of exposure 8 weeks
Source: compiled during the evaluation

6.21 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with guanfacine + long-acting stimulant in comparison to placebo + long-acting stimulant, over a duration of exposure of 8 weeks.:

- Approximately 16 additional patients would achieve symptomatic remission
- Approximately 11 would be classified as a responder (defined as an ADHD-RS-IV reduction of ≥25%)
- Approximately a 4.70 point greater reduction in the ADHD-RS-IV total score was achieved. Note, this may not represent a clinically significant change in ADHD-RS-IV total score.
- Approximately 6 additional patients would have abdominal pain (upper) and 9 additional patients would have somnolence.

Table 8: Summary of comparative benefits and harms for guanfacine and atomoxetine*

Benefits						
Symptomatic remission (ADHD-RS-IV total score ≤18)						
Trial	**Guanfacine**	**Atomoxetine**	**RR (95% CI)**	**Events/100 patients***		**RD (95% CI)**
				Guanfacine	**Atomoxetine**	
Trial 316	57/112	38/112	**1.50 (1.09, 2.06)**	50.9	33.9	**0.17 (0.04, 0.30)**
Responder (reduction in ADHD-RS-IV of ≥30% and CGI-I ≤2)						
Trial 316	72/112	62/112	1.16 (0.94, 1.44)	64.3	55.4	0.09 (-0.04, 0.22)
Mean change in ADHD-RS-IV scores						

Trial	**Guanfacine**			**Atomoxetine**			**Mean difference* (95% CI)**
	n	**Mean Δ**	**SD**	**n**	**Mean Δ**	**SD**	
Trial 316	112	-23.9	12.41	112	-18.6	11.91	**-5.30 (-8.49, -2.11)**

Harms						
	Guanfacine	**Atomoxetine**	**RR (95% CI)**	**Events/100 patients***		**RD (95% CI)**
				Guanfacine	**Atomoxetine**	
Somnolence						
Trial 316	50/114	20/112	**2.46 (1.59, 3.87)**	43.9	17.9	**0.26 (0.14, 0.37)**
Nausea						
Trial 316	18/114	30/112	**0.59 (0.35, 0.98)**	15.8	26.8	**-0.11 (-0.21, -0.003)**

*Trial 316 duration of exposure 13 weeks

6.22 On the basis of direct comparison evidence presented by the submission, for every 100 patients treated with guanfacine in comparison to atomoxetine, over a duration of exposure of 13 weeks:

- Approximately 17 additional patients would achieve symptomatic remission.
- A similar number of patients would be classified as a responder (defined as an ADHD-RS-IV reduction of ≥30% and a CGI-I ≤2).

- Approximately a 5.30 point greater reduction in the ADHD-RS-IV total score would be achieved. Note, this may not represent a clinically significant change in ADHD-RS-IV total score.
- Approximately 26 additional patients would experience somnolence.
- Approximately 11 fewer patients would experience nausea.

Clinical claim

6.23 The submission described guanfacine as superior in terms of comparative effectiveness and as "having a trend towards [comparative] inferior safety" over atomoxetine in patients who are "contraindicated to stimulant therapy or are switching to guanfacine monotherapy due to poor tolerability". The claim regarding comparative safety was reasonable however the claim regarding comparative effectiveness may not be reasonable as:

- The comparison of guanfacine and atomoxetine was not the primary comparison of the trial and was conducted post-hoc;
- The patients enrolled in Trial 316 were not entirely representative of the requested population as they were not required to have contraindications or be intolerant to stimulants for enrolment;
- Although a statistically significant greater reduction in ADHD-RS-IV scores was observed for those treated with guanfacine compared with those treated with atomoxetine, the clinical significance of the difference was uncertain; and
- No statistically significant differences in the proportion of responders (defined as ADHD-RS-IV total score reduction ≥30% and a CGI-I ≤2), were observed between treatments, but a statistically significantly greater proportion of patients treated with guanfacine achieved "symptomatic remission" (defined as ADHD-RS-IV total score ≤18).
- The ESC noted the submission adopted an assumption of non-inferiority in taking a cost-minimisation approach in the economic analysis.

6.24 The submission described guanfacine in combination with stimulant therapy as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo in combination with stimulant therapy in patients who "intend to support the use of guanfacine as add-on therapy in patients who have an unsatisfactory response on optimal stimulant therapy". This claim was reasonable in terms of comparative safety, however, the claim of superior effectiveness may not be reasonable as:

- Although a statistically significant greater reduction in ADHD-RS-IV scores was observed for those treated with guanfacine + long-acting stimulants compared with those treated with placebo + long-acting stimulants, the clinical significance of the difference was uncertain.
- It was however noted that a statistically significantly greater proportion of patients treated with guanfacine + long-acting stimulants also achieved "responder"

(defined as ADHD-RS-IV total score reduction ≥25%) and "symptomatic" (defined as ADHD-RS-IV total score ≤18) and "syndromal" (defined as ADHD-RS-IV total score ≤18 AND CGI-S ≤2) remission status, compared with those treated with placebo + long-acting stimulants.

6.25 Although the submission suggested that guanfacine could be used as monotherapy among those who have failed to achieve an adequate response to stimulants, the submission did not provide a clinical claim for this population. The trials informing a comparison of guanfacine monotherapy and placebo enrolled patients with or without a history of prior stimulant use (ranging from 18.5% to 73.3% of patients with prior stimulant use). Thus, as discussed above for "patients who are intolerant of stimulants", any clinical claim made for use of guanfacine as monotherapy would require acceptance that the comparative effectiveness and safety versus placebo observed in a broader ADHD population would also apply to those who are achieving an inadequate response to stimulants.

6.26 The PBAC considered that the claim of superior comparative effectiveness over atomoxetine was questionable, but noted the submission requested listing on a cost-minimisation basis with atomoxetine, and a claim of non-inferiority to support listing on that basis was adequately supported, for patients who are contraindicated or intolerant to stimulants.

6.27 The PBAC considered the claim of a trend towards inferior, comparative safety compared to atomoxetine for patients who are contraindicated or intolerant to stimulant therapy was adequately supported.

6.28 The PBAC considered the claim of superior comparative effectiveness over placebo as adjunctive therapy in patients who have an inadequate response to stimulant therapy may be supported for adjunctive therapy, but the extent of benefit was unclear.

6.29 The PBAC considered the claim of inferior comparative safety compared to placebo as adjunctive therapy in patients who have an inadequate response to stimulant therapy was adequately supported.

6.30 The PBAC noted the submission did not make an explicit clinical claim for guanfacine as monotherapy in patients who had an inadequate response to stimulant therapy, and further noted that no evidence to support a listing in this population was presented.

Economic analysis

6.31 The submission presented (i) a cost-minimisation analysis versus atomoxetine for patients who are contraindicated or intolerant to stimulants and (ii) a cost-utility analysis for treatment with guanfacine + long-acting stimulants versus placebo + long-acting stimulants in patients who fail to achieve an adequate response to stimulant therapy.

(i) Cost-minimisation analysis versus atomoxetine

6.32 The trial-based equi-effective doses are estimated as guanfacine 3.6mg per day (or 1.19 tablets) up to 13 weeks and atomoxetine 42.1mg per day (or 1.08 capsules) for up to 13 weeks based on the results of Trial 316.

6.33 The submission estimated that the average daily dose of atomoxetine in Australian clinical practice is 34.17 mg/day and 1.31 capsules from a 10% PBS sample. Very little information is provided with respect to the population used in the analysis, although it appeared to be based on 67 patients who were dispensed at least two prescriptions of atomoxetine. The submission noted that this dosing was lower than that observed in Trial 316 (42.1mg/day) and suggested this may have been due to (i) the trial not including titration doses, estimation of equi-effective doses should be based on 'steady state' dosing (p208 of the PBAC Guidelines v4-5); and (ii) the patients in Trial 316 tended to be older than the PBS population taking atomoxetine. In the PSCR (p3) the sponsor provided more details on the 10% PBS sample and indicated that the sample used was concessional patients only, who were naïve to ADHD medication. The ESC considered that both these criteria could lead to a non-representative sample given there is likely to be large use in non-concessional patients, and patients naïve to ADHD medication could only represent the use of atomoxetine on the PBS for patients contraindicated to stimulants and not those who are intolerant to stimulants.

6.34 The submission requested a relativity of guanfacine 1.19 tablets/day (from Trial 316) and atomoxetine 1.31 capsules/day (derived from a 10% PBS sample). Based on a weighted average ex-manufacturer price of $[redacted]/day for atomoxetine, the submission derived an effective DPMQ of $[redacted].

6.35 The submission did not explicitly provide a justification for requesting this relativity, but it was presumably to incorporate the "current" use of atomoxetine in Australia. The PSCR (p3) argued that the cost-minimisation analysis based on the relative number of capsules/tablets per patient per day rather than the total dose per day was appropriate given the flat pricing structure of atomoxetine (and proposed for guanfacine) on the PBS and that the Study 316 protocol artificially lowered the number of capsules per day; whereas in clinical practice approximately 30% of patients treated with atomoxetine adopt twice daily dosing to reduce side-effects. There are numerous concerns with the approach taken in estimating the average doses and capsules/day of atomoxetine based on this 10% PBS sample and in the derivation of the cost/day. However, even if the atomoxetine dose and capsules/day were estimated appropriately, the dose of guanfacine (and average tablets per day) required in this population to achieve non-inferior outcomes is unknown.

6.36 A cost-minimisation analysis based on the relativity of guanfacine 1.19 tablets/day and 1.08 atomoxetine capsules/day and a weighted average ex-manufacturer price of $[redacted]/day for atomoxetine, results in an effective DPMQ of $[redacted]. The ESC considered that equi-effective doses based on the trial doses were appropriate. The PBAC agreed with the ESC and considered a cost-minimisation analysis based on equi-effective doses derived from the trials was appropriate.

(ii) a cost-utility analysis for treatment with guanfacine + long-acting stimulants versus placebo + long-acting stimulants in patients who fail to achieve an adequate response to stimulant therapy

6.37 A summary of model structure presented in the submission and rationale is presented in Table 9. The model presented in the submission was based on the model presented in the lisdexamfetamine submissions considered at the July 2013 and July 2014 PBAC meetings. The key differences between the models are (i) the time horizon (limited to one year in the current submission compared with five years previously) and (ii) differences in the definition of response (symptomatic response defined as ADHD-RS-IV ≤18 (i.e. remission) compared with a reduction of 50% or more on the ADHD rating scale and a score of 1 (much improved) or 2 (improved) on the clinician-rated CGI-I previously). The ESC considered an economic analysis based on responder definitions, rather than remission, may have been informative as this will include the health benefits of participants who are improving substantially from very severe illness but not quite reaching the cut-off of ADHD-RS-IV ≤18.

Table 9: Summary of model structure and rationale

Component	Summary
Time horizon	1 year in the model versus 8 weeks in the trial for initial response rates. Maintenance of response was derived from a long-term extension study (Study 318, enrolling patients from Trials 315 and 316) where 2-year guanfacine discontinuation rates were reported
Outcomes	Quality-adjusted-life-years (QALYs).
Methods used to generate results	A Markov cohort expected value analysis
Health states	Responder/non-responder. Base case: responder defined as symptomatic remission (ADHD-RS-IV ≤18), with responder defined as syndromal remission (ADHD-RS-IV ≤18 & CGI-S ≤2) and ADHD-RS-IV reduction of ≥25% in sensitivity analyses.
Utilities	Utility values for responder and non-responder health states ([redacted] and [redacted]) are taken from Trial 325 based upon comparable definitions of 'response' with Trial 313.
Cycle length	28 days
Transition probabilities	Initial response from Trial 313 (8 week trial) and discontinuation rates derived from a two-year long-term study (Study 318)

Source: Section D of the submission

6.38 Table 10 summarises the key inputs and assumptions driving the outputs of the model.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Treatment effect (definition of responder)	Base case defines responders based on symptomatic remission (ADHD-RS-IV ≤18). Defining responder by an ADHD-RS-IV reduction of ≥25% significantly increases the ICER. The PSCR (p4) stated that using an absolute threshold to define response is more appropriate as it attaches quality of life and QALYs to the severity of, rather than a change in, symptoms experienced by the patient. As noted above, ESC considers this may not account for health benefits of participants who are improving substantially from very severe illness but not quite reaching the cut-off of ADHD-RS-IV ≤18.	High, favours guanfacine
Utilities	High values for model health states taken from a lisdexamfetamine trial (Trial 325) – [redacted] for responder and [redacted] for non-responder in the base case. Issues with the derivation of these utilities have been considered before when they were used in the July 2013 lisdexamfetamine submission. Use of alternative values has a significant effect on the ICER. No disutility for AEs. The utilities based on responders (e.g. ADHD-RS-IV ≥30% & CGI-I of 1 or 2) may better reflect the utilities associated with treatment responses (responder=[redacted]; non-responder=[redacted]).	High, favours guanfacine
Cost	The model excludes drug and non-drug costs associated with titration of guanfacine to optimal doses and excluded cost that would be associated with dose tapering at discontinuation.	High, favours guanfacine

Source: compiled during the evaluation

6.39 Table 11 presents the results of the stepped economic evaluation presented in the submission. The price derived from the cost-minimisation analysis of guanfacine versus atomoxetine ($[redacted]) was the assumed price for guanfacine in the model. The base case ICER was $45,000/QALY - $75,000/QALY which compares to the ICER for atomoxetine in the second-line treatment of ADHD of between ($15,000 and $45,000/QALY (Atomoxetine PSD, November 2006)). These results include the incorrect cost per day for methylphenidate, assumed to be $[redacted] rather than $[redacted]. The ICER increases slightly to $45,000/QALY - $75,000/QALY when assuming a daily cost of $[redacted].

Table 11: Results of the stepped economic evaluation from the submission

Step and component	GXR+LA S	PBO+LA S	Increment
Step 1: Cost per responder at 4 weeks			
Costs (drug-costs only)	$[redacted]	$[redacted]	$[redacted]
Probability of response	0.616	0.461	0.155
Incremental cost per responder			$[redacted]
Step 2: Extrapolation to 1 year			
Costs	$[redacted]	$[redacted]	$[redacted]
Probability of response	0.580	0.434	0.146
Incremental cost per responder			$[redacted]
Step 3: Include health-state costs			
Costs	$[redacted]	$[redacted]	$[redacted]
Probability of response	0.580	0.434	0.146

		Incremental cost per responder	$[redacted]
Step 4: Transform health-states to QALYs			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	0.8841	0.8706	0.0135
		Incremental cost/QALY	$[redacted]

Source: Table D-14, page 209 of the submission
GXR=guanfacine, PBO=placebo, LA S=long-acting stimulant

6.40 Using the DPMQ derived from the cost-minimisation analysis conducted during the evaluation ($[redacted]) and assuming a daily cost of $[redacted] for methylphenidate results in an ICER of $45,000/QALY - $75,000/QALY.

6.41 The submission conducted a series of univariate sensitivity analyses and further univariate and multivariate analyses were conducted during the evaluation. The ICER was most sensitive to the definition of responder used, utility values assumed for responder and non-responder and inclusion of estimated drug and non-drug costs associated with guanfacine titration. Table 12 summarises key sensitivity analysis results varying the definition of response and using different utilities.

6.42 The ESC considered a reasonable alternative base case could define response as ADHD-RS-IV total score reduction ≥25% and use utilities based on ADHD-RS-IV improvement of ≥30% and a CGI-I score of 1 or 2. The ESC acknowledged that utilities were available from trial 325 where responders where classified by ADHD-RS-IV ≥30%. However it was felt these were likely to be optimistic utilities. The results of this alternative economic analysis resulted in an ICER of $105,000 - $200,000 per QALY when the guanfacine price was adjusted for the corrected price of modified release methylphenidate (see highlighted sensitivity analysis in Table 12).

6.43 The PBAC noted the advice of the ESC, which considered that using a definition of 'responder' (defined by a 25% improvement in ADHD-RS-IV score) may be a more appropriate basis for the economic model. The PBAC also noted the advice of provided during the sponsor hearing, which clarified the importance of remission (defined by an ADHD-RS-IV score ≤18) in patient outcomes, and considered that the use of remission rates in the economic model is appropriate.

Table 12: Results of univariate and multivariate sensitivity analyses, adjusting definition of response and utilities applied

	Incremental cost-effectiveness (ICER) ($ per QALY)	
	Submission	Correcting Concerta® cost[a] and guanfacine DPMQ[b]
Base case – Symptomatic remission Responder: ADHD-RS-IV ≤18 Utilities: R= ; NR=	$	$
Definition of response		
Syndromal remission Responder: ADHD-RS-IV total score ≤18 AND CGI-S ≤2 Utilities: R= ; NR=	$	$
Responder Responder: ADHD-RS-IV total score reduction ≥25% Utilities: R= ; NR=	$	$
Utility values: reported in Trial 325 where response defined as ADHD-RS-IV ≥30% & CGI-I of 1 or 2		
Symptomatic remission Responder: ADHD-RS-IV ≤18 Utilities: R= ; NR=	$	$
Syndromal remission Responder: ADHD-RS-IV total score ≤18 AND CGI-S ≤2 Utilities: R= ; NR=	$	$
Responder Responder: ADHD-RS-IV total score reduction ≥25% Utilities: R= ; NR=	$	$
Utility values: reported in Trial 325 where response defined as ADHD-RS-IV ≥30%		
Symptomatic remission Responder: ADHD-RS-IV ≤18 Utilities: R= ; NR=	$	$
Syndromal remission Responder: ADHD-RS-IV total score ≤18 AND CGI-S ≤2 Utilities: R= ; NR=	$	$
Responder Responder: ADHD-RS-IV total score reduction ≥25% Utilities: R= ; NR=	$	$

Source: Table D-15 of submission (page 211-212) & additional analyses conducted by evaluator
R=responder; NR=non-responder
[a] cost of Concerta® applied as $ per day in submission's model, should be $
[b] DPMQ of $ for guanfacine

Drug cost/patient/year: $

6.44 Drug cost/patient/year was derived from the requested effective DPMQ: $/28*1.19*365 (assuming % take one tablet and % take two tablets per day) or $ based on a DPMQ of $. This compares with $ (assuming 80mg or 100mg atomoxetine capsule per day ($/28*365)) or $ for atomoxetine 10-60mg formulations ($/56*1.3*365; assuming % take one capsule and % take two capsules per day).

Estimated PBS usage & financial implications

6.45 This submission was not considered by DUSC.

6.46 Table 13 summarises the estimated use and financial implications of listing guanfacine.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of guanfacine					
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$4[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for atomoxetine, clonidine					
Cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications					
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

[a] Assuming number of scripts per year as estimated by the submission.
Source: Section E of the submission

The redacted table shows that at year 5, the estimated number of scripts is 100,000-200,000 and the net cost to the PBS would be less than $10 million per year.

6.47 There is a potential for the number of scripts of guanfacine to be different to those estimated in the submission.

- The estimates only include patients aged 6-17 years inclusive, should 18 year olds also be eligible, the estimates are underestimated.
- The estimates of guanfacine scripts are a likely underestimated as the titration phase for guanfacine (and other therapies) has not been accounted for.
- There is potential that patients who initiate on clonidine and stimulants + clonidine (assuming they are using clonidine for the treatment of ADHD) may be contraindicated or intolerant to stimulants (relevant to the former group) or require clonidine as add-on due to a suboptimal response to stimulants (relevant to the latter group), making them eligible for treatment with guanfacine. Their exclusion from the estimates would therefore result in the number of guanfacine scripts being underestimated.
- It is not known how many patients who are currently taking stimulants are achieving a suboptimal response, thus the assumption of [redacted]% may be under- or over-estimated.
- The submission's estimates do not account for the possibility that guanfacine may be used concomitantly with short-acting stimulants, thus the estimates may be underestimated.

- There is no long-term data to indicate whether guanfacine may have an impact on growth. It is possible that doses of stimulants may be decreased to limit exposure due to their known impact on growth or other adverse events, with the potential to add-on guanfacine. The estimates do not account for this, thus the estimates may be underestimated.

Overall, the net impact of these uncertainties on the likely use of guanfacine is unknown. The ESC considered on the balance of these uncertainties, the utilisation and financial estimates were likely to be underestimated.

6.48 The assumption of no impacts on other government health budgets may not be reasonable as:

- the titration phase for guanfacine, which could be for up to 7 weeks, has not been accounted for. This phase may be associated with additional specialist visits for determining response for dose optimisation, which would lead to differential resource use; and
- guanfacine was associated with different adverse events compared with atomoxetine and a number of adverse events occurred statistically significantly more often when guanfacine was added to stimulant therapy compared with no add-on treatment. These differences in adverse event profiles may also lead to differential resource use.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

7.1 The PBAC recommended the listing of guanfacine on a cost-minimisation basis with atomoxetine for the treatment of patients with attention deficit hyperactivity disorder (ADHD) who are contraindicated or intolerant to stimulant therapy. The PBAC did not recommend the listing of guanfacine as adjunctive therapy in patients who have failed to achieve an adequate response to stimulants given the uncertain clinical significance of the trial outcomes and the uncertain cost-effectiveness. The PBAC did not recommend the listing of guanfacine as monotherapy in patients who have failed to achieve an adequate response to stimulants as the evidence presented did not support a listing in that population.

7.2 The PBAC noted the comments in the sponsor hearing and agreed there was a clinical place for guanfacine as an alternative treatment option to atomoxetine for patients who are contraindicated or intolerant to stimulants. The PBAC also considered there may be a clinical place for guanfacine as add-on therapy for the small sub-set of patients with an inadequate response to stimulants. However, PBAC noted that 'a satisfactory response' and 'optimised stimulant therapy' are broad definitions, which may be difficult to implement and contain to the [redacted]% of patients requiring

adjunct therapy to achieve remission, as identified in the sponsor hearing as the patient group likely to benefit from adjunctive therapy.

7.3 The PBAC considered that the restrictions for guanfacine for the recommended indications should be aligned with the current listings of atomoxetine. The PBAC recommended that, similar to atomoxetine, guanfacine for these indications should be a streamlined authority.

7.4 The PBAC noted the submission requested that guanfacine be restricted to patients 17 years and younger. The Committee noted the clinician input at the sponsor hearing, which described that there was limited evidence for patients aged 18 and over, and agreed that restricting guanfacine in such a way that patients may be forced to discontinue treatment at 18 years of age would create challenges for prescribers and patients. The Committee noted that initiation of atomoxetine was restricted to patients under the age of 18, but that continuing restrictions permitted patients to continue on treatment without age restrictions.

7.5 The PBAC accepted that atomoxetine was the appropriate comparator for patients who are contraindicated or intolerant to stimulant therapy. The PBAC also accepted placebo as the appropriate comparator for patients who have an inadequate response to stimulant therapy, either as adjunctive or monotherapy, although other stimulants would also be an appropriate comparator. The PBAC did not accept clonidine as an informative secondary comparator in this population as it is neither TGA registered nor PBS listed in Australia for the treatment of ADHD, and thus its safety, efficacy and cost-effectiveness are unknown.

7.6 The PBAC noted the claim of superior comparative effectiveness with atomoxetine was questionable given Trial 316 did not specifically recruit patients intolerant or contraindicated to stimulants and the comparison with atomoxetine was post-hoc. Over 50% of patients in Trial 316 were treatment naïve and only a small proportion of those would have been contraindicated for stimulants. Of the remaining 49.6% who did take prior stimulants, only 37.1% had intolerable side effects. However, despite these applicability and statistical power issues, the PBAC noted the data for remission and mean change in ADHD-RS-IV scores favoured guanfacine, and by taking a cost-minimisation approach in the economic analysis the submission adopted an assumption of non-inferiority. The PBAC accepted this as reasonable.

7.7 The PBAC considered the claim of a trend towards inferior comparative safety over atomoxetine was reasonable.

7.8 The PBAC noted that for adjunctive therapy, Trial 313 showed statistically significant improvements for guanfacine over placebo for all outcomes, although the clinical significance of the change in ADHD score was uncertain. The PBAC did not accept the clinical data for guanfacine monotherapy versus placebo provided any basis for accepting monotherapy use among those who have failed to achieve an adequate response to stimulants.

7.9 The PBAC accepted the claim of inferior comparative safety over placebo in combination with stimulant therapy.

7.10 For the cost-minimisation to atomoxetine, the PBAC noted the submission argued that analysis based on the relative number of capsules/tablets per patient per day rather than the total dose per day was appropriate given the flat pricing structure of atomoxetine (and proposed for guanfacine) on the PBS. However, the PBAC considered the 10% PBS sample used by the submission to establish equi-effective doses was unreliable. The PBAC also noted the reduced price offered in the pre-PBAC response (pp. 2-3) weighted the dosing across the trial data and clinical practice data, but again considered the reliance on the 10% PBS sample was fraught. The PBAC accepted the equi-effective doses from the trial data, as calculated during the evaluation, to be the most relevant; the equi-effective doses are guanfacine 3.6mg per day (or 1.19 tablets) up to 13 weeks and atomoxetine 42.1mg per day (or 1.08 capsules) for up to 13 weeks, based on the results of Trial 316.

7.11 The PBAC noted the cost-utility analysis used to calculate the ICER was based on the same model used in the lisdexamfetamine submission, with some changed parameters, including the time horizon and use of remission rates rather than response rates. Noting the clinician opinion at the sponsor hearing, the Committee considered the use of remission rate was an appropriate basis for the economic model, however, the PBAC noted the sensitivity of the model to the alternative base case provided by the ESC. The PBAC considered the sensitivity of the model to the outcome used and the difficulty in containing the eligible population under the proposed restriction meant that overall the ICER was not acceptable at the price proposed. Even using the reduced price calculated during the evaluation from the cost-minimisation to atomoxetine, the ICER of $45,000/QALY-$75,0000/ QALY was considered uncertain and unacceptable.

7.12 The PBAC considered that the utilisation and financial estimates were probably underestimated, and was concerned that how guanfacine would be used in practice was unclear. In particular, the PBAC noted that the dose titration period was not accounted for in the estimates, and the different adverse event profiles of guanfacine and atomoxetine created uncertainty around substitution and use of these therapies in practice. As an add-on to stimulants, the PBAC considered the assumption of [redacted]% of patients currently taking stimulants achieving a suboptimal response may be reasonable, but would likely underestimate uptake given the clinician discretion is assessing when the response is inadequate and stimulant use is optimal.

7.13 The PBAC considered that a minor submission with a lower price with no other amendments to the economic model for the adjunctive therapy indication for patients who have an inadequate response to stimulant therapy would be required to address the issue of uncertain cost-effectiveness in this population. The PBAC also considered that as this would likely result in a weighted price scenario for the listings of

guanfacine, that new financial estimates would be required as part of any resubmission.

7.14 The PBAC advised that guanfacine should not be treated as interchangeable on an individual basis with any other drugs.

7.15 The PBAC advised that guanfacine is not suitable for prescribing by nurse practitioners.

7.16 The PBAC recommended that the Early Supply Rule should apply.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended – Patients contraindicated or intolerant to stimulant therapy

Rejected – Add-on or monotherapy in patients who have an inadequate response to stimulants

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
GUANFACINE				
Tablet containing guanfacine hydrochloride 1 mg, 28	1	5		
Tablet containing guanfacine hydrochloride 2 mg, 28	1	5	Intuniv®	Shire Australia Pty Limited
Tablet containing guanfacine hydrochloride 3 mg, 28	1	5		
Tablet containing guanfacine hydrochloride 4 mg, 28	1	5		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Attention deficit hyperactivity disorder
PBS Indication:	Attention deficit hyperactivity disorder
Treatment phase:	Initial

Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Treatment criteria:	Must be treated by a paediatrician or psychiatrist
Clinical criteria:	• The condition must be or have been diagnosed according to the DSM-5 criteria **AND** • Patient must have a contraindication to dexamfetamine, methylphenidate or lisdexamfetamine as specified in TGA-approved product information; **OR** • Patient must have a comorbid mood disorder that has developed or worsened as a result of dexamfetamine, methylphenidate or lisdexamfetamine treatment and is of a severity necessitating treatment withdrawal; **OR** • Patient must be at an unacceptable medical risk of a severity necessitating permanent stimulant treatment withdrawal if given a stimulant treatment with another agent; **OR** • Patient must have experienced adverse reactions of a severity necessitating permanent treatment withdrawal following treatment with dexamfetamine, methylphenidate and lisdexamfetamine (not simultaneously).
Population criteria:	Patient must be or have been diagnosed between the ages of 6 and 17 years inclusive.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Attention deficit hyperactivity disorder
PBS Indication:	Attention deficit hyperactivity disorder
Treatment phase:	Continuing
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's comment

Shire will continue to work with the Department of Health so that patients with ADHD may access guanfacine on the PBS.