7.15 GUANFACINE
Modified release tablet containing guanfacine hydrochloride 1 mg, 2 mg, 3 mg, 4 mg, Intuniv®, Shire Australia Pty Limited

1 Purpose of Application

1.1 The minor resubmission sought a listing of guanfacine for the treatment of attention deficit hyperactivity disorder (ADHD) as add-on therapy in certain patients who have failed to achieve an adequate response to optimised stimulant therapy.

1.2 The PBAC previously recommended guanfacine for the treatment of ADHD as monotherapy in patients who are contraindicated or intolerant to stimulants at its July 2017 meeting.

2 Requested listing

2.1 The resubmission requested the following additional listing to include treatment as add-on therapy in combination with stimulants for ADHD.

2.2 Limited suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
GUANFACINE HYDROCHLORIDE					
Modified release tablet, 1 mg, 28	1	5	$[redacted] (Effective)	Intuniv®	Shire Australia Pty Ltd
Modified release tablet, 2 mg, 28	1	5	$[redacted] (Weighted effective)		
Modified release tablet, 3 mg, 28	1	5	$123.72 (Published)		
Modified release tablet, 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 treatment

Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	The condition must be or have been diagnosed by a paediatrician or psychiatrist according to the DSM-5 criteria; AND Patient must be receiving a maximum tolerated dose (MTD) of stimulant (dexamphetamine, methylphenidate or lisdexamfetamine) which has been stable for at least four weeks; AND Patient must be experiencing residual moderate to severe ADHD symptoms resulting in impaired functioning, present in at least one setting; AND The treatment must be adjunctive to ongoing MTD of stimulant
Population criteria:	Patient must be or have been diagnosed between the ages of 6 and 18 years inclusive.
Definitions:	Setting refers to the physical location, for example, home, nursery/school/college/work, friends or family homes or other environment; Functional impairment may be social, academic or occupational.

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 treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	~~Patient must have previously been issued with an authority prescription for this drug~~ *Patient must have previously received PBS-subsidised treatment with this drug for this condition in this setting.* *AND* *The treatment must be adjunctive to ongoing maximum tolerated dose of stimulant (dexamphetamine, methylphenidate or lisdexamfetamine)*

2.3 The pre-PBAC response noted two alternative restrictions that were more prescriptive in measuring residual ADHD symptoms with regards to determining patient eligibility. The PBAC considered a restriction which permitted some flexibility in allowing clinicians to select appropriate therapies was reasonable.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Background

3.1 Guanfacine was TGA registered in August 2017 and is indicated for "the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants). Guanfacine must be used as part of a comprehensive ADHD management programme, typically including psychological, educational and social measures."

3.2 In July 2017, the PBAC recommended guanfacine for monotherapy in patients who are contraindicated or intolerant to stimulants. The recommendation was made on a cost-minimisation basis with atomoxetine (paragraph 7.1, July 2017 PSD). Guanfacine is not yet PBS-listed in this setting.

3.3 In July 2017, the PBAC rejected guanfacine for add-on/adjunctive therapy in patients who have failed to achieve an adequate response to stimulants on the basis of uncertain clinical significance of the trial outcomes and uncertain cost effectiveness (paragraph 7.1, July 2017 PSD). The minor resubmission requested listing in this setting.

3.4 In July 2017, the PBAC also rejected guanfacine for 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 (paragraph 7.1, July 2017 PSD). This indication was not requested in this minor resubmission.

Previous PBAC consideration in add-on setting

3.5 In its previous consideration the PBAC stated 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…..and 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" (paragraph 7.13, July 2017 PSD).

3.6 Key changes compared with the previous submission were:

- A [redacted]% lower effective DPMQ was proposed in the add-on setting ($[redacted] versus $[redacted] in the previous submission). This was also [redacted] The definition of sub-optimal response was revised in the requested restriction;
- Updated financial estimates were provided;
- A weighted price was proposed based on predicted utilisation in the add-on versus monotherapy settings (based on a weighting of [redacted]% versus [redacted]%, respectively to derive a weighted effective DPMQ of $[redacted]).

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

4.1 The minor resubmission nominated placebo as the primary comparator. This was previously accepted by the PBAC. The previous submission nominated clonidine as a secondary comparator. This was not accepted by the PBAC as clonidine is neither TGA registered nor PBS listed in Australia for the treatment of ADHD, and thus its safety, efficacy and cost-effectiveness are unknown (paragraph 7.5, July 2017 PSD).

4.2 The Secretariat noted that whilst clonidine was not a secondary comparator in the resubmission, it formed part of the utilisation estimates for guanfacine monotherapy and its inclusion increased the weighted price that was calculated (see the Estimates of utilisation and financial implications and weighted price estimate sections below).

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

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

Clinical trials

5.3 No new clinical trials or clinical evidence were presented in the minor resubmission. The submission re-presented the outcomes of Trial 313, the pivotal trial used in the original submission to support the add-on therapy indication. Trial details and associated publications are re-presented from the July 2017 Public Summary Document below.

Table 1: Trials and associated reports presented in the re-submission

Trial ID	Protocol title/Publication title	Publication citation
Direct randomised trial		
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

Source: Guanfacine July 2017 Public Summary Document

Comparative effectiveness

5.4 The submission re-presented a summary of proportions of patients achieving symptomatic *response* and symptomatic *remission,* as shown in the table below.

Table 2: Summary of efficacy measures from Trial 313 (trial of use in combination with stimulants)

Guanfacine + stimulant vs placebo + stimulant			
Continuous outcomes	**MD [95%CI]; p-value** ***(A negative result favours guanfacine + stimulant)***		
Mean change from baseline in ADHD-RS-IV total score at endpoint	-4.70 [-7.05, -2.35]; < 0.0001		
Mean change from baseline in Oppositional Subscale score of the CPRS-R:L at endpoint	-2.20 [-3.60, -0.80]; 0.002		
Dichotomous outcomes	**RD [95% CI]; p-value**	**RR [95% CI]; p-value**	**OR [95% CI]; p-value**
	RD > 0 favours guanfacine + stimulant	***RR/OR > 1 favours guanfacine + stimulant***	
Proportion of subjects classified as a responder (at least a 25% reduction in ADHD-RS-IV total score at endpoint)	0.11 [0.03, 0.20]; 0.009	1.16 [1.03, 1.31]; 0.01	1.87 [1.19, 2.93]; 0.007
Proportion of subjects achieving symptomatic remission (ADHD-RS-IV total score of ≤18 at endpoint)	0.16 [0.06, 0.25]; 0.002	1.34 [1.10, 1.62]; 0.003	1.88 [1.27, 2.79]; 0.002
Proportion of subjects achieving syndromal remission (ADHD-RS-IV total score of ≤18 and CGI-S ≤2 at endpoint)	0.14 [0.05, 0.23]; 0.003	1.47 [1.11, 1.94]; 0.007	1.83 [1.20, 2.77]; 0.005
Proportion of subjects with CGI-S score ≤ 2 (normal/borderline mentally ill) at endpoint	0.14 [0.05, 0.23]; 0.004	1.42 [1.10, 1.84]; 0.007	1.79 [1.19, 2.70]; 0.005
Proportion of subjects with CGI-I score ≤ 2 (very much improved/much improved) at endpoint	0.14 [0.05, 0.24]; 0.002	1.25 [1.07, 1.46]; 0.004	1.91 [1.27, 2.87]; 0.002

Source: Guanfacine minor submission (Table 6, p15)

ADHD-RS-IV: Attention Deficit Hyperactivity Disorder-Rating Scale IV; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; CI: confidence interval; CPRS-R:L: Conners' Parent Rating Scale-Revised Long Form; GXR: guanfacine extended release; MD: mean difference; PBO: placebo; OR: odds ratio; RD: risk difference; RR: relative risk; S: stimulant

Comparative harms

5.5 The PBAC previously considered that compared with placebo + long-acting stimulants, those treated with guanfacine + stimulants were statistically significantly more likely to experience any treatment-emergent adverse event, somnolence, headache, sedative event, abdominal pain (upper) and fatigue (paragraph 6.18, July 2017 PSD).

Benefits and harms

5.6 The submission did not present new clinical evidence. The benefits and harms summary for the add-on therapy indication (guanfacine + stimulants vs. placebo + stimulants) has been reproduced from the July 2017 Public Summary Document below.

Table 3: Summary of comparative benefits and harms for guanfacine and placebo* (July 2017 PSD): based on use in combination with stimulants only

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	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	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	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	25/302	3/153	**4.22 (1.39, 13.04)**	8.3	2.0	**0.06 (0.02, 0.10)**
Somnolence						
Trial 313	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: Guanfacine July 2017 Public Summary Document

5.7 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; and
- Approximately 6 additional patients would have abdominal pain (upper) and 9 additional patients would have somnolence.

Clinical claim

5.8 The resubmission repeated its clinical claim from the July 2017 submission and described guanfacine, in combination with stimulant therapy, as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo when used in combination with stimulant therapy in patients who have an unsatisfactory response on optimised stimulant therapy.

5.9 In its previous consideration, the PBAC noted that for add-on 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 (paragraph 7.8, July 2017 PSD).

5.10 The PBAC accepted the claim of inferior comparative safety over placebo in combination with stimulant therapy (paragraph 7.9, July 2017 PSD).

Economic analysis

5.11 The minor resubmission updated its economic analysis using a lower price for guanfacine in the add-on therapy setting (DPMQ of $[redacted] versus $[redacted] in the previous submission).

5.12 The PBAC, in its July 2017 consideration, explicitly requested that any resubmission for the add-on indication should include a lower price and no other amendments to the economic model. A comparison of the economic incremental cost-effectiveness ratios (ICERs) between the two submissions is presented in the table below. The change in DPMQ was the only amendment made to the model.

Table 4: Summary of ICERs from original submission, revised base case and current resubmission

	Guanfacine + stimulant	Stimulant	**Increment**
July 2017 base case (DPMQ = $[redacted])			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	0.8841	0.8706	0.0135
ICER			$[redacted]/QALY
July 2017 respecified base case after Commentary/ESC suggestions (DPMQ = $[redacted])			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	0.8841	0.8706	0.0135
ICER			$[redacted]/QALY
July 2018 base case (DPMQ = $[redacted])			
Costs	$[redacted]	$[redacted]	$[redacted]
QALYs	0.8841	0.8706	0.0135
ICER			**$[redacted]/QALY**

Source: Table 9, p19 of the minor resubmission
DPMQ = dispensed price for maximum quantity; ESC = Economic Sub-Committee; ICER = incremental cost-effectiveness ratio; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life year
Note: the base case result presented in the 'July 2017 base case' row of this table is based on the model presented in the original submission (original submission, Table D-13). Results in the 'July 2017 respecified base case' row were based on modifications suggested in the Commentary and the ESC advice. These changes were documented in the July 2017 pre-PBAC response to the ESC advice: the price of methylphenidate increased from $2 to $2.29; titration resource use costs in guanfacine patients were included; and there was revised implementation of half cycle correction (Shire pre-PBAC response, Table 1).

5.13 Using the updated requested effective DPMQ ($[redacted]), resulted in an ICER of $15,000/QALY – $45,000/QALY. This compared to a respecified base case of $45,000/QALY - $75,000/QALY in the July 2017 submission.

Drug cost/patient/year: $[redacted] (weighted effective DPMQ)

5.14 The drug cost per patient per year was calculated assuming 100% single tablet use (as used in the financial estimates below), a 28 tablet pack size and the weighted

effective DPMQ (see Weighted price estimate section below), which resulted in the following calculation: $[redacted] * 365.

5.15 Using the effective DPMQ proposed for the add-on therapy setting, of $[redacted], the drug cost per patient per year was calculated to be $[redacted]. These calculations assumed single tablet use only (while the previous submission, and the estimates in monotherapy, assumed that [redacted]% of patients were on one tablet a day and [redacted]% were on two tablets per day).

Estimated PBS usage & financial implications

5.16 In its consideration of the utilisation and financial estimates of guanfacine as an add-on therapy in July 2017 (paragraphs 6.2, 7.12 and 7.13, July 2017 Public Summary Document (PSD)), the PBAC:

- Noted that the dose titration period was not accounted for. This was not addressed in the resubmission;
- Considered the assumption that 10% of patients currently taking stimulants achieve a suboptimal response may be reasonable, but would likely underestimate uptake given the clinician discretion in assessing when the response is inadequate and stimulant use is optimal. The PBAC also noted that the clinician presenting at the sponsor hearing stated that [redacted]–[redacted]% of patients do not achieve an optimal response to stimulants. An assumption of 20% was used in the resubmission; and
- Recommended that new financial estimates would be required in order to calculate a weighted price (see Weighted price estimate section below).

5.17 The resubmission presented revised financial estimates in both the add-on and monotherapy settings. The table below outlines the changes compared with the previous submission in each of these settings. In summary, the previous estimates included some parameters that were general to both the monotherapy and add-on settings, while in the resubmission some revised assumptions were applied that were specific to each of the settings. The resubmission then compared the estimated utilisation in the add-on setting versus the monotherapy setting to derive a weighted price.

Table 5: Comparison of financial assumptions in the previous submission (July 2017) versus the current resubmission (monotherapy and add-on presented separately)

Previous submission	Resubmission - monotherapy setting	Resubmission – add-on setting
Patient age		
Only included patients **aged 6-17 years** (inclusive)	**Includes all ages** *(recommendation allows continuation >17 years of age).* Uptake rates differed by age (see below): - For atomoxetine and clonidine 75% of patients were assumed to be aged 6-17 years.	**Includes all ages** Uptake rates differed by age (see below): - For stimulants 80% of patients were assumed to be aged 6-17 years. *The difference vs monotherapy was based on age distributions from PBS utilisation data for stimulants vs atomoxetine/clonidine*
Forecast ADHD market growth		
Based on linear growth of atomoxetine, clonidine and methylphenidate from 2010/11 to 2015/16 (applied to each drug separately). Lisdexamfetamine growth was based on methylphenidate SR. Avg. growth over 5 years was: Monotherapy market: 5% Stimulant market: 7.5%	Monotherapy market: **7%** in Years 1 to 6 Based on atomoxetine and clonidine from 2011/12 to 2016/17.	Stimulant market: **12.5%** in Years 1 to 6 Based on methylphenidate and lisdexamfetamine from 2011/12 to 2015/16. *Note this included lisdexamfetamine which was listed in 2015/16.*
Conversion to patient years: Number of packs required for 12 months treatment		
Drug / **Packs/12 months** Guanfacine [redacted]* Atomoxetine [redacted]** Clonidine [redacted] Methylphenidate [redacted] Lisdexamfetamine [redacted] * Based on Trial 316 ** Weighted average usage of 56 and 28 packs, 2015/16	**Drug** / **Packs/12 months** **Guanfacine** [redacted] ([redacted] tabs/day) Atomoxetine [redacted]* Clonidine [redacted] * Weighted average usage of 56 and 28 packs, 2016/17 *(i.e. the change in atomoxetine scripts was due to updated PBS data being used)*	**Drug** / **Qty/ pack** / **Packs/ 12 months** **Guanfacine** / **28** / [redacted]* Methylphenidate / 30 / [redacted] Lisdexamfetamine / 30 / [redacted] * 1 tablet/day in add-on therapy *Max. dose is lower in add-on (4 mg/day) vs. monotherapy (7 mg/day in adolescents), so lower dose may be appropriate in this setting.*
Proportion of population eligible for guanfacine		
In monotherapy, would replace: - [redacted]% of atomoxetine use; - [redacted]% of clonidine use Used as add-on in **10%** of patients on methylphenidate or lisdexamfetamine	In monotherapy, would replace: - [redacted]% of atomoxetine use *(unchanged)* - [redacted]% of clonidine use *(appeared to be updated to address previous concerns that this was underestimated [b])*	Used as add-on in **20%** of patients on methylphenidate or lisdexamfetamine
Uptake rates for guanfacine		
Both add-on and monotherapy: **Yr 1** / **Yr 2** / **Yr 3** / **Yr 4** / **Yr 5** [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]%	**Year 1** / **Year 2** / **Year 3** / **Year 4** / **Year 5** [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]% *Differences to previous submission due to:* - *half-year uptake was applied in Year 1.* - *lower uptake assumed in patients aged >17 years [a] (assumed >17 year olds would be continuing patients only)*	**Year 1** / **Year 2** / **Year 3** / **Year 4** / **Year 5** [redacted]% / [redacted]% / [redacted]% / [redacted]% / [redacted]% *Higher uptake versus monotherapy is because fewer patients were assumed to be >17 years in the add-on setting (based on PBS utilisation data for long-acting stimulants).*
DPMQ		
Effective DPMQ: $[redacted]	Effective DPMQ: $[redacted]. *The sponsor is requested to update this in its Pre-PBAC response.*	Effective DPMQ: $[redacted] Weighted effective DPMQ: $[redacted]

ADHD = attention deficit hyperactivity disorder; ADJ = adjunctive therapy; DPMQ = dispensed price for maximum quantity; MONO = monotherapy; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Qty = quantity; SR = sustained-release

Note: Other minor changes included: co-payments were updated in the resubmission based on 2016/17 utilisation data (rather than 2015/16).

[a] Uptake outside 6-17 year age group was estimated to be: Year 1: [redacted]%; Year 2: [redacted]%; Year 3: [redacted]%; Year 4: [redacted]%; Year 5: [redacted]%. The resubmission (p25) stated that lower uptake rates were used as these patients would be continuing rather than switching.

[b] *The previous Minutes stated that "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." (paragraph 6.47, July 2017 PSD). The financial estimates spreadsheet ('Assumptions – Pops and Prices' worksheet cells K87-88) stated the change was because the "analysis included all patients who use clonidine as a second line treatment (switch or mono) after the failure of prior treatments."*

Add-on therapy setting

5.18 The resubmission used a market share approach to inform the utilisation and financial estimates of guanfacine for use as an add-on therapy in combination with stimulants (methylphenidate or lisdexamfetamine).

5.19 As shown in the table below, to estimate the extent of use, the following broad approach was taken:

- Current utilisation of the stimulants was determined from PBS utilisation data and projected to Year 6 using the observed average annual growth rate for stimulants (methylphenidate and lisdexamfetamine) from the previous five years to 2015/2016. This resulted in an annual growth rate of 12.5% per annum. This may have overestimated utilisation of stimulants as this included 2015/16 when lisdexamfetamine was first PBS-listed, so growth during this period may be attributed to the availability of lisdexamfetamine on the PBS. A recent DUSC analysis (May 2018) showed that the total ADHD market grew by an average of 10% per annum over the five years from 2013 to 2017. However, the DUSC analysis did not include separate analyses of growth in monotherapy and add-on therapy. The DUSC analysis also noted that the increase in growth of overall ADHD medicines supplied may be attributed to the listing of lisdexamfetamine in September 2015 and a lack of offset from substitution of other ADHD medicines.
- Utilisation of methylphenidate and lisdexamfetamine was converted to patient years of therapy by dividing the projected utilisation by [redacted] items per patient year (pack size of 30, full compliance).
- 20% of patients on stimulant therapies were assumed to be eligible for guanfacine add-on therapy. This was increased from 10% in the previous submission and was the upper limit (10%-20%) of patients noted by the PBAC who would require adjunct therapy to achieve remission (paragraph 7.2, July 2017 PSD). The Secretariat noted that this assumption (using the higher estimate) was conservative (and likely appropriate) in the context of estimating a weighted price.

- Uptake rates were then applied to estimate the total number of patient years. Lower uptake rates were assumed than in the previous submission as the resubmission included patients outside the TGA-approved age group of 6-17 years in whom lower uptake was assumed.
- Patients receiving guanfacine as add-on therapy were assumed to receive one tablet per day, or [redacted] prescriptions per year (pack size of 28, full compliance). This was lower than in the monotherapy setting (where 1.19 tablets per day were assumed). This difference may have been appropriate as the maximum recommended dose is lower in add-on therapy and lower doses may be expected when used in combination. However, the guanfacine dose titration period was not accounted for which may have underestimated use as wastage or multiple tablets per day maybe required during this time.

5.20 The table below shows the estimated use and financial implications of listing guanfacine on the PBS/RPBS.

Table 6: Estimated use and financial implications of listing guanfacine as an add-on to stimulant therapy

		Method	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use								
A	Projected utilisation of stimulants	12.5% x PBS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B	Patient years of therapy	A / [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C	Eligible population (patient years)	B x 20%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	Uptake rates	Assumption	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
E	ADJ guanfacine (patient years)	C x D	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F	**Total ADJ guanfacine scripts**	**E x** [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous submission – July 2017								
	Total ADJ guanfacine scripts [a]	**-**	[redacted] [b]	[redacted]	[redacted]	[redacted]	[redacted]	-
Estimated net financial implications of ADJ guanfacine to the PBS/RPBS (adjusted for co-payment of $16.64)								
Using effective DPMQ ($[redacted])			$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Using weighted effective DPMQ ($[redacted])			$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Using published DPMQ ($[redacted])			$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Previous submission – July 2017								
ADJ setting: Using effective DPMQ ($[redacted] minus copay of $14.74)			$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	-

Source: Table 12, p24 of the resubmission, Utilisation and financial estimates of the resubmission and *calculated during evaluation*

ADJ = adjunctive therapy; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] *Based on 'Market share analysis' worksheet, Rows 52+53 of GXR_BudgetImpact_MAR2017.XLSX from the previous submission.*

[b] *Note that Year 1 in the previous submission was 2017/18, while it was 2018/19 in the resubmission (thus baseline script numbers were higher in the resubmission due to an extra year of growth).*

5.21 Using the effective price, the minor resubmission estimated listing guanfacine on the PBS as add-on therapy would result in a net cost to the PBS/RPBS of less than $10 million in Year 1, rising to less than $10 million in Year 6, with a total net cost of $10 - $20 million over the first 6 years.

5.22 Using the weighted effective price proposed in the resubmission (see below for calculations) the listing of guanfacine to the PBS as add-on therapy would result in a net cost to the PBS/RPBS of less than $10 million in Year 1, rising to less than $10 million in Year 6, with a total net cost of $20 - $30 million over the first 6 years.

5.23 Higher utilisation was estimated in the resubmission (50,000 – 100,000 scripts in Year 5 in the resubmission versus 10,000 – 50,000 in the previous submission) due to the application of higher market growth, inclusion of patients outside the 6-17 year age range and the higher estimated eligible population (20% of patients on stimulants were assumed to be eligible versus 10% in the previous submission).

5.24 The Secretariat notes that utilisation in the add-on setting may differ to that estimated as:

- Guanfacine dose titration was not accounted for (underestimated use).
- Underlying market growth may have been overestimated (potentially overestimated use).
- The estimates did not account for the possibility that guanfacine may be used concomitantly with short-acting stimulants (underestimated use). The resubmission stated that such use was unlikely, and it is noted that only long-acting stimulants were used concomitantly in the trial.
- 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 (as noted in paragraph 6.47, July 2017 PSD). The estimates do not account for this, thus the estimates may be underestimated.

5.25 The Secretariat noted that underestimation of utilisation in the add-on setting would result in the derivation of a higher than reasonable price in the weighted price calculations (as a lower DPMQ was proposed in the add-on setting).

Use in the monotherapy setting (used to derive weighting)

5.26 In order to calculate a weighted price estimate, the utilisation of guanfacine as monotherapy was re-estimated using a market share approach. This broadly consisted of:

- Determining the current utilisation of atomoxetine and clonidine (for ADHD only) from PBS utilisation data and projecting these to 2023/2024, by applying a growth rate of 7% per annum, which was the average observed growth rate for atomoxetine and clonidine over the previous five years.

- Utilisation was converted to patient years of therapy. For atomoxetine the projected utilisation was divided by [redacted] items per patient year; for clonidine utilisation was divided by [redacted].
- [redacted]% of atomoxetine patients were assumed to be eligible for guanfacine monotherapy as the PBS listings were essentially identical. [redacted]% of clonidine patients were assumed to be eligible for monotherapy with guanfacine; this was based on a 10% PBS sample as presented in the July 2017 submission. The PBAC previously considered that the different adverse event profiles of guanfacine and atomoxetine created uncertainty around substitution and use of these therapies in practice (paragraph 7.12, July 2017 PSD). Further, the assumption of substitution from clonidine may not be appropriate (as discussed further below).
- Uptake rates were then applied to estimate the total number of patient years.
- The submission assumed that patients receiving guanfacine as monotherapy would receive 1.19 tablets per day, or [redacted] prescriptions per year. Per the estimates in add-on therapy, the guanfacine dose titration period was not accounted for.

5.27 The Secretariat notes that in recommending guanfacine for monotherapy in patients who were contraindicated or intolerant to stimulant therapy in July 2017, the PBAC accepted atomoxetine as the appropriate comparator (paragraph 7.5, July 2017 PSD). Clonidine was **not** nominated as a comparator in this population. For the add-on therapy indication, the July 2017 PBAC accepted placebo as the appropriate primary comparator. The July 2017 submission nominated clonidine as a secondary comparator; however, this was not accepted by the PBAC in this population as it is neither TGA registered nor PBS listed (paragraph 7.5, July 2017 PSD). Thus, the assumed uptake from clonidine may not be appropriate.

Table 7: Estimated utilisation of monotherapy guanfacine

		Method	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of guanfacine monotherapy use								
A	Projected utilisation of ATOM	7% x PBS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B	Patient years of therapy	A / [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C	Eligible population of ATOM (patient years)	B x [redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D	Projected utilisation of CLON	7% x PBS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
E	Patient years of therapy	D / [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F	Eligible population of CLON (patient years)	E x [redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G	ATOM + CLON eligible population	C + F	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H	Uptake rates of guanfacine	Assumption	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
I	MONO guanfacine (patient years)	G x H	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
J	**Total MONO guanfacine scripts**	**I x** [redacted]	[redacted] [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Previous submission – total scripts [b]			[redacted] [a]	[redacted]	[redacted]	[redacted]	[redacted]	-
Estimated extent of guanfacine monotherapy use – no clonidine substitution								
K	*MONO guanfacine scripts*	*C x H x* [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Utilisation and financial estimates of the submission and *calculated during evaluation*
ATOM = atomoxetine; CLON = clonidine; MONO = monotherapy; PBS = Pharmaceutical Benefits Scheme
[a] *Compared with the previous submission, the resubmission estimated a lower number of scripts in Year 1, because a half-year uptake rate was applied in the first year (whereas the previous submission applied a full year uptake rate in Year 1).*
[b] *Year 1 in the previous submission was 2017/18, while it was 2018/19 in the resubmission (thus baseline script numbers were higher in the resubmission due to an extra year of growth).*

5.28 Higher total utilisation was estimated in the resubmission compared with the previous submission (100,100 – 200,000 scripts in Year 5 in the resubmission versus 50,000 – 100,000 in the previous submission). This is due to the inclusion of patients outside the 6-17 year age range and the use of more recent PBS utilisation data to estimate the size and growth of the ADHD market (which included an additional year of growth).

5.29 The Secretariat noted that a significant amount (approximately [redacted]%) of expected guanfacine use in the monotherapy population was from patients who treatment switched from off-label use of clonidine. This increased the utilisation estimates in the monotherapy population, and this had a direct impact on the proportions used in the weighted price calculation below. If substitution from clonidine were to be considered appropriate for estimating utilisation in the monotherapy setting, its inclusion in the weighted price calculations may remain inappropriate. It may reduce the comparability of the estimates between the two settings as the eligible

population in the add-on setting did not include patients on clonidine (e.g. a higher uptake rate could have been used for patients currently on clonidine plus stimulants).

Weighted price

5.30 The expected utilisation of guanfacine as monotherapy and add-on therapy over the first five years of listing was used to calculate a weighting and the effective weighted price, as outlined below.

Table 8: Weighted effective price calculations

	Total scripts, Years 1-5	Weighting	Effective AEMP	Effective DPMQ
Monotherapy guanfacine	[redacted]	[redacted]%	$[redacted]	$[redacted]
Add-on therapy guanfacine	[redacted]	[redacted]%	$[redacted]	$[redacted]
Weighted price			**$[redacted]**	**$[redacted]**
Weighted effective price – no clonidine substitution				
Monotherapy guanfacine	[redacted]	[redacted]%	$[redacted]	$[redacted]
Add-on therapy guanfacine	[redacted]	[redacted]%	$[redacted]	$[redacted]
Weighted price			***$[redacted]***	***$[redacted]***

Source: Utilisation and financial estimates of the submission and *calculated during evaluation*
AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity

5.31 The resubmission assumed that [redacted]% of guanfacine scripts would be in the monotherapy setting and [redacted]% in the add-on setting. This resulted in a weighted effective price of $[redacted] (DPMQ). The calculation used a price for guanfacine in the monotherapy setting that was stated to be [redacted] at the time the minor submission was prepared. The Secretariat notes that the final weighted price would be calculated using the most current price of guanfacine in the monotherapy setting.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended the listing of guanfacine, as a General Schedule Authority Required (Streamlined) benefit, as add-on therapy in conjunction with optimised stimulant therapy, for attention deficit hyperactivity disorder (ADHD) in patients experiencing residual moderate to severe ADHD symptoms.

6.2 The PBAC was satisfied that guanfacine (as add-on therapy) provides, for some patients, a significant improvement in efficacy over placebo in patients receiving optimised stimulant therapy and who are experiencing residual symptoms.

6.3 The PBAC recalled it has previously considered the results of Trial 313 of guanfacine as add-on therapy in conjunction with optimised stimulant therapy, and reaffirmed its previous conclusions that guanfacine (as add-on therapy) was of superior comparative effectiveness and inferior comparative safety compared to placebo in

the clinical place requested in the resubmission. The PBAC accepted there was a clinical place for guanfacine in an adjunctive setting for patients who continue to experience moderate or severe residual ADHD symptoms who are also on optimised stimulant therapy.

6.4 The PBAC noted the requested restriction and sponsor comments in its Pre-PBAC response, and considered it would be appropriate for the restriction to allow some flexibility for clinicians to individually evaluate patient responses to stimulant therapy and determine whether they may benefit from guanfacine add-on therapy. Therefore, the PBAC considered the proposed criteria defining ADHD symptoms was appropriate as requested.

6.5 The PBAC recalled it had previously accepted placebo as the appropriate comparator.

6.6 The PBAC noted the resubmission offered a [redacted]% lower price (AEMP $[redacted] for the add-on setting), which resulted in an ICER of $15,000/QALY - $45,000/QALY, approximately [redacted]% lower than the previous submission. The PBAC considered the ICER was high for this population; however was acceptable based on the clinical need for additional therapies in patients who experience residual symptoms whilst on optimised stimulant therapy.

6.7 The PBAC noted the submission used a weighted price calculation between the monotherapy and add-on therapy populations to determine a final price of guanfacine. The PBAC considered there were some uncertainties as to how the weightings were calculated ([redacted]% from monotherapy, [redacted]% from add-on therapy), particularly as the submission included a substantial population assumed to be receiving off-label clonidine in the monotherapy setting, which favoured a higher weighted price. The PBAC noted that if clonidine in the monotherapy population was removed from the weighted price calculations, the dispensed price of guanfacine would decrease from $[redacted] to $[redacted]. However, on balance, it was considered the weighting as requested by the sponsor was probably reasonable, as the submission had also taken more conservative estimates of uptake in the add-on therapy setting (20%, up from 10% in the original submission) and larger increases in the stimulant therapy market than the monotherapy market. The PBAC noted the price may alter further to reflect the final agreed price in the monotherapy population listing on the PBS for that indication.

6.8 The PBAC considered there was some uncertainty in the utilisation and financial estimates, in particular concerning the off-label use of clonidine in ADHD and of the extent of potential substitution. The PBAC agreed a risk share arrangement (RSA) with a hard cap on PBS expenditure based on the submission estimates would be a reasonable method to mitigate the risk of higher than expected use of guanfacine.

6.9 The PBAC advised that guanfacine is not suitable for prescribing by nurse practitioners, similar to other drugs used in the treatment of ADHD.

6.10 The PBAC recalled it had previously advised that guanfacine should not be treated as

interchangeable with any other drugs and reaffirmed its previous advice.

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

6.12 The PBAC advised the Department of Health to correspond with State and Territory health departments advising of the recommendation of guanfacine as add-on therapy, as individual states and territories have different controls and prescribing requirements regarding stimulants for ADHD.

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

Outcome:
Recommended

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
GUANFACINE HYDROCHLORIDE				
Modified release tablet, 1 mg, 28	1	5	Intuniv®	Shire Australia Pty Ltd
Modified release tablet, 2 mg, 28	1	5		
Modified release tablet, 3 mg, 28	1	5		
Modified release tablet, 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 treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	The condition must be or have been diagnosed by a paediatrician or psychiatrist according to the DSM-5 criteria; AND Patient must be receiving a maximum tolerated dose (MTD) of stimulant (dexamphetamine, methylphenidate or lisdexamfetamine) which has been stable for at least four weeks; AND Patient must be experiencing residual moderate to severe ADHD symptoms resulting in impaired functioning, present in at least one setting; AND The treatment must be adjunctive to ongoing MTD of stimulant
Population criteria:	Patient must be or have been diagnosed between the ages of 6 and 18 years inclusive.
Definitions:	Setting refers to the physical location, for example, home, nursery/school/college/work, friends or family homes or other environment; Functional impairment may be social, academic or occupational.

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 treatment
Restriction Level / Method:	☐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 for this condition in this setting.* *AND* *The treatment must be adjunctive to ongoing maximum tolerated dose of stimulant (dexamphetamine, methylphenidate or lisdexamfetamine)*

8 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.

9 Sponsor's Comment

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