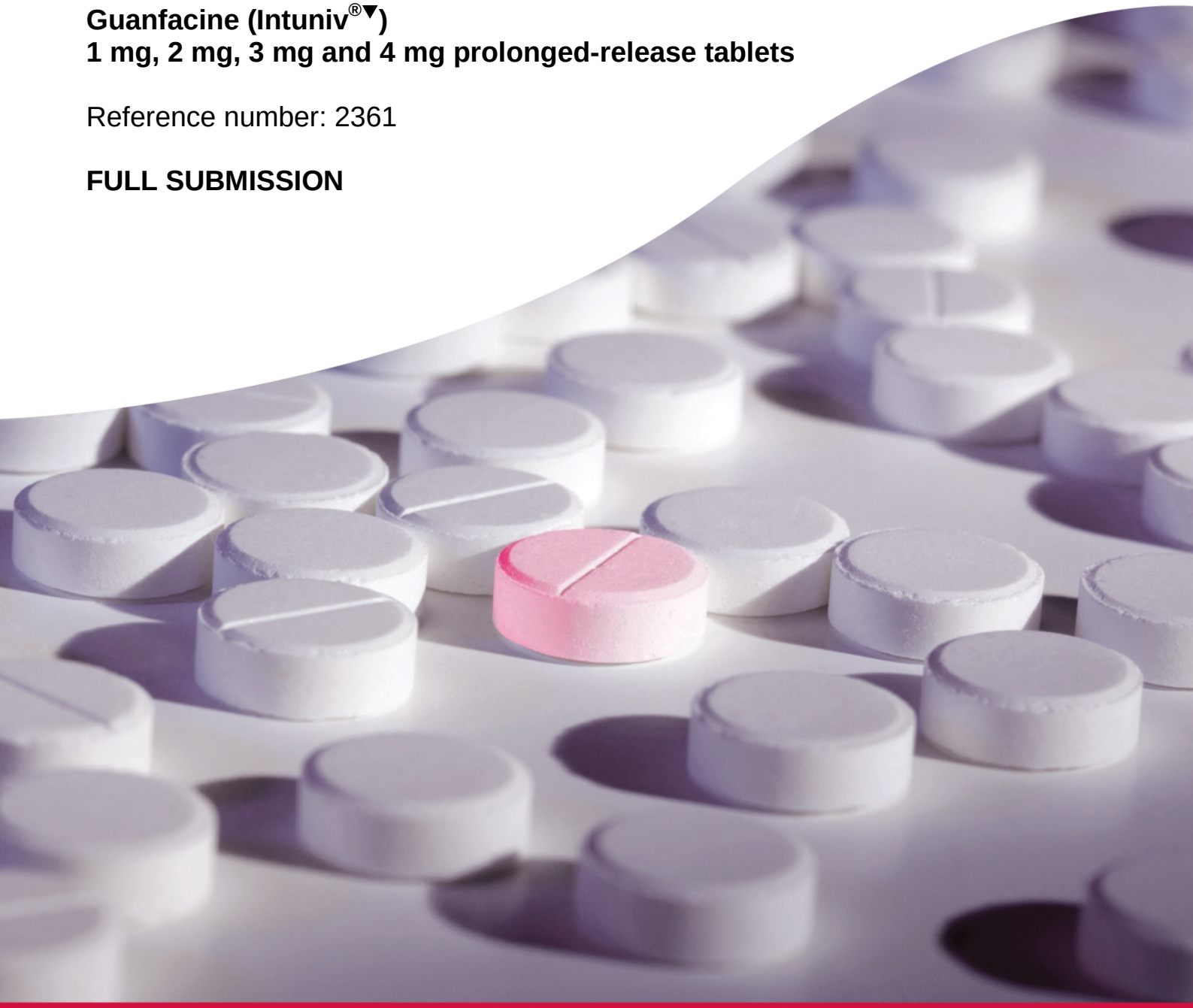
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Guanfacine (Intuniv®▼)
1 mg, 2 mg, 3 mg and 4 mg prolonged-release tablets

Reference number: 2361

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Guanfacine (Intuniv®▼) 1 mg, 2 mg, 3 mg and 4 mg prolonged-release tablets

This assessment report is based on evidence submitted by Shire Pharmaceuticals Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Guanfacine (Intuniv®▼) for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Guanfacine must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures[2].
Dosing	Careful dose titration and monitoring is necessary at the start of treatment. The recommended starting dose is 1 mg of guanfacine, taken orally once a day. The dose may be adjusted in increments of not more than 1 mg per week. Depending on the patient's response and tolerability for guanfacine the recommended maintenance dose range is 0.05-0.12 mg/kg/day. Refer to the Summary of Product Characteristics (SPC) for further information including pre-treatment screening, monitoring and dose titration[2].
Marketing authorisation date	17 September 2015[2].

2.0 DECISION CONTEXT

2.1 Background

Attention deficit/hyperactivity disorder (ADHD) is a heterogeneous neurobehavioural disorder characterised by impulsivity, hyperactivity and inattention (either alone or in combination)[3,4]. Treatments for ADHD include psychological, behavioural, educational, dietary and/or pharmacological interventions[3]. Where treatment with medication is considered appropriate, clinical Guideline 72 (CG72) issued by the National Institute for Health and Care Excellence (NICE) advises that healthcare professionals should consider methylphenidate first-line, or atomoxetine in the presence of some comorbid conditions; where methylphenidate has been tried and has been ineffective at the maximum tolerated dose; or where the child or young person is intolerant to low or moderate doses of methylphenidate. Dexamfetamine should be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine[3].

Guanfacine (as hydrochloride) (Intuniv®▼) is a prolonged-release (PR) non-stimulant treatment for ADHD[2]. The mode of action of guanfacine PR in ADHD is not fully understood; however, non-clinical data suggests it modulates signalling in the prefrontal cortex and basal ganglia through direct modification of synaptic noradrenalin transmission at the alpha2-adrenergic receptors[2,4]. At the time of writing, atomoxetine was the only other licensed non-stimulant treatment for ADHD.

2.2 Comparators

The comparator included in the company submission was atomoxetine (Strattera®).

2.3 Guidance and related advice

- NICE. CG72. Attention deficit hyperactivity disorder: diagnosis and management (2013)[3].
- NICE. Quality Standard 39. Attention deficit hyperactivity disorder (2013)[5].
- NICE. Technology Appraisal 98. Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents (2006)[6].

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of atomoxetine (Strattera®)[7], lisdexamfetamine dimesylate (Elvanse Adult®)[8] and lisdexamfetamine dimesylate (Elvanse®)[9].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company included information from a clinical study programme consisting of ten phase III studies that examined the efficacy and safety of guanfacine PR in children and/or adolescents[1]. Two studies, SPD503-315 and SPD503-316, contained mixed EU/North American patient populations and were considered by the company to be pivotal studies. Both were placebo-controlled studies of guanfacine PR; however, SPD503-316 included an active reference arm of atomoxetine. SPD503-316 was not statistically powered to detect a difference between guanfacine PR and atomoxetine; therefore, the company included a mixed treatment comparison (MTC)[1]. The remaining eight studies in the clinical programme enrolled only patients from North America and will not be discussed in detail.

3.1 Study SPD503-316

SPD503-316 was a randomised, double-blind, multicentre, parallel-group, placebo-controlled, dose-optimisation study, with an active reference arm of atomoxetine[1,2,4,10]. Patients (aged 6–17 years) had a diagnosis of ADHD of at least moderate severity, defined by a baseline ADHD Rating Scale version IV (ADHD-RS-IV: see Glossary for measures) with a total score of 32 or higher, and a minimum Clinical Global Impression-Severity (CGI-S) score of 4[10]. Of the 338 patients randomised (1:1:1) to guanfacine PR (1–7 mg as tablets), atomoxetine (40–100 mg as capsules) or placebo, 337 were evaluated to assess once daily dosing (children: n = 242; adolescents: n = 95), all of whom met the DSM-IV-TR® criteria for ADHD[1,2,4]. Study medication was dosed in a double-dummy design and administered in line with the Summary of Product Characteristics (SPC)[2,10,11]. The total study treatment duration (after the screening period) was 10 weeks for children (6–12 years) and 13 weeks for adolescents (13–17 years) and included a dose-optimisation and maintenance phase. Dose titration was permitted during the dose-optimisation phase (four weeks for patients aged 6–17 years and seven weeks for patients 13–17 years). Patients who achieved ≥ 30% reduction in ADHD-RS-IV total score from the baseline visit (visit 2/week 0) and a Clinical Global Impressions-Improvement (CGI-I) of 1 or 2 at a given tolerated dose were considered to be at an optimal dose. The use of at least one prior stimulant medication was reported by approximately 50% of all patients[1,10].

The primary efficacy endpoint was the change from baseline in ADHD-RS-IV total scores at visit 15 (week 10 for children and week 13 for adolescents)[1,2,4,10]. The key secondary endpoints were improvement in the CGI-I rating scale, change from baseline in Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) for the learning and school domain, and the family domain, and improvement in the Health Utility Index – Mark 2 and Mark 3 (HUI-2/3), all at visit 15[1,4,10]. In addition, a pre-specified analysis of various ADHD responder definitions was performed (≥ 25%, ≥ 30% or ≥ 50% reduction in ADHD-RS-IV score from baseline).

Results are presented in Table 1. Mean ADHD-RS-IV total scores were similar across treatment groups at baseline[1,2,4,10]. Mean change from baseline to visit 15 was greater for guanfacine PR and atomoxetine compared with placebo. Results of the key secondary endpoints (CGI-I and WFIRS-P) were overall supportive of the primary endpoint[1,2,10]. At visit 15 (week 10/13), the mean ± SD HUI-2/3 multi-attribute utility scores remained similar across the treatment groups (approximately 0.92).

Table 1. Results of primary and secondary endpoints in study SPD503-316 (full analysis set)[1,10].

Measure	Guanfacine PR (n = 114)	Atomoxetine (n = 112)	Placebo (n = 111)
ADHD-RS-IV*			
Baseline mean (SD) score	43.1 (5.47)	43.7 (5.86)	43.2 (5.60)
Mean (SD) change from baseline to visit15 LOCF	−23.9 (12.41)	−18.6 (11.91)	−15.0 (13.07)
Difference from placebo (95% CI) in LS means	−8.9 (−11.9 to −5.8) p < 0.001	−3.8 (−6.8 to −0.7) p = 0.017	NA
Mean (95% CI) change from baseline to visit 15 LOCF, guanfacine PR versus atomoxetine†	−5.1 (−8.2 to −2.0) p = 0.001		NA
CGI-I§			
Improvement¶, n (%)	76 (67.9)	63 (56.3)	49 (44.1)
Difference from placebo (95% CI) in % improved	23.7 (11.1 to 36.4) p < 0.001	12.1 (−0.9 to 25.1) p = 0.024	NA
WFIRS-P§			
Difference from placebo (95% CI) in LS means, learning and school domain	−0.22 (−0.36 to −0.08) p = 0.003	−0.16 (−0.31 to −0.02) p = 0.026	NA
Difference from placebo (95% CI) in LS means, family domain	−0.21 (−0.36 to −0.06) p = 0.006	−0.09 (−0.24 to −0.06) p = 0.242	NA
ADHD-RS-IV responder analysis**			
Proportion of responders at visit 15 (%)	64.3	55.4	42.3
Difference from placebo	p < 0.001	p = 0.017	NA

* Primary endpoint.
† Pre-specified secondary analysis (not controlled for multiplicity).
§ Secondary endpoint.
¶ Improvement includes CGI-I categories “very much improved” and “much improved”.
** A responder was defined as a subject who demonstrated a percentage reduction from baseline in the ADHD-RS-IV total score of ≥ 30% and a CGI-I of 1 or 2.

ADHD-RS-IV: attention deficit hyperactivity disorder Rating Scale version IV; CGI-I: Clinical Global Impressions-Improvement rating scale; CI: confidence interval; LOCF: last observation carried forward; LS: least squares; NA: not applicable; PR: prolonged-release; SD: standard deviation; WFIRS-P: Weiss Functional Impairment Rating Scale-Parent.

3.2 Study SPD503-315

SPD503-315 was a double-blind, placebo-controlled, multicentre, randomised withdrawal, long-term maintenance study designed to assess the efficacy, safety, and tolerability of once-daily, optimised dosing of guanfacine PR in children and adolescents aged 6–17 years[1,2,4]. Of the 528 patients randomised (1:1) to guanfacine PR (1–7 mg) or placebo, 503 were assessed in a seven-week open-label dose optimisation phase (children: n = 376; adolescents: n = 127); on completion all patients entered a six-week open-label maintenance period at the optimal dose. Of these, 301 patients met the protocol defined response criteria and were assessed in the following 26-week, double-blind, randomised-withdrawal phase (guanfacine PR: n = 150; placebo: n = 151)[1]. All patients met the DSM-IV-TR® criteria for ADHD. The use of at

least one prior stimulant medication was reported by approximately 64% of all patients[1].

The primary efficacy endpoint was the proportion of cumulative treatment failures that occurred among patients during the withdrawal phase (see Glossary for measures)[1,2,4]. Secondary endpoints included time to treatment failure, ADHD-RS-IV total score, Clinical Global Impressions-Severity (CGI-S) rating scale and WFIRS-P[1].

At visit 23 (week 39), less patients in the guanfacine PR group (n = 74 [49.3%]) were categorised as treatment failures compared with patients in the placebo group (n = 98 [64.9%]) at a statistically significant level (treatment difference: −15.6 [95% confidence interval: −26.6 to −4.5]; p = 0.006)[1,4]. Results of secondary endpoints were generally supportive of the primary endpoint. The WFIRS-P scores, however, did not demonstrate an improvement in functioning[1,4].

3.3 MTC

In order to address the lack of direct comparative evidence, the company included a systematic literature review and MTC to assess the efficacy and safety of guanfacine PR and other treatments for ADHD in children (aged 6–12 years) and adolescents (aged 13–17 years). Treatments included monotherapy lisdexamphetamine, methylphenidate-immediate or extended release, atomoxetine, clonidine immediate release, guanfacine immediate release and guanfacine PR[1]. Outcomes reported included ADHD-RS-IV change from baseline, CGI-I response, all-cause discontinuation and adverse event (AE) discontinuation.

In total, 31 randomised controlled studies met the screening criteria and were included in the MTC analyses and 6 additional short term studies were included in sensitivity analyses. The company report assessments of heterogeneity and also compared fixed effects and random effects models. The results of the fixed effects model (deemed to be the best fit) for ADHD-RS-IV change from baseline and CGI-I response are presented in Table 2. The company conclude that numerically guanfacine PR demonstrated consistently favourable results compared to atomoxetine[1].

Table 2. Results of the fixed effects model for ADHD-RS-IV change from baseline and CGI-I response[1].

Treatment	Mean/OR (95% CrI)	Probability of treatment being most effective	Probability of guanfacine PR being more effective
ADHD-RS-IV change from baseline (medicine versus placebo): 20 RCTs			
Guanfacine PR	−8.76* (−10.25 to −7.24)	0.00%	–
Lisdexamfetamine	−14.92* (−16.58 to −13.26)	100.00%	< 1%
Atomoxetine	−6.95* (−7.96 to −5.95)	0.00%	97.86%
Methylphenidate extended-release	−9.16* (−10.68 to −7.62)	0.00%	35.56%
CGI-I response (medicine versus placebo): 13 RCTs			
Guanfacine PR	3.52† (2.58 to 4.81)	< 1%	–
Lisdexamfetamine	9.11† (6.23 to 13.57)	99.80%	< 1%
Atomoxetine	2.74† (1.88 to 4.05)	< 1%	87.93%
Methylphenidate extended-release	4.37† (3.06 to 6.30)	< 1%	19.65%
Methylphenidate immediate-release	2.42† (1.50 to 3.90)	<1%	88.59%

* Mean.
† Odds ratio.

ADHD-RS-IV: Attention Deficit/Hyperactivity Disorder Rating Scale-IV; CGI-I: Clinical Global Impressions-Improvement; CrI: credible interval; OR: odds ratio; PR: prolonged-release; RCTs: randomised controlled trial.

3.4 Comparative safety

At the time of licensing, evidence for clinical safety (safety population defined as all patients who received at least one dose) was pooled from 17 studies of ADHD patients aged 6–17 years treated with guanfacine PR (n = 2411) and 14 studies of healthy adult volunteers (n = 486)[4]. The company highlight that study SPD503-316 is pivotal for the indication under consideration and safety results are summarised below; however, results for the other individual studies presented in the company submission are summarised together as part of the pooled analysis considered by the EMA. The company state that results of the MTC for all-cause discontinuation and AE discontinuation were broadly in favour of guanfacine PR compared to atomoxetine.

3.4.1 Study SPD503-316

More patients in the guanfacine PR group experienced AEs than patients in the atomoxetine or placebo groups (88 [77.2%], 76 [67.9%], and 73 [65.8%], respectively)[1]. The majority of AEs were mild or moderate intensity. Somnolence was the most common AE (guanfacine PR: n = 50 [43.9%]; atomoxetine: n = 20 [17.9%]; placebo: n = 16 [14.4%]). The other most common AEs in the guanfacine PR group were headache, fatigue, abdominal pain, nausea, decreased appetite, dizziness, insomnia, and increased appetite. AEs of special interest included sedative events which were reported in 44.7%, 18.8% and 14.4% of patients in the guanfacine PR, atomoxetine, and placebo groups, respectively. More patients in the guanfacine PR group experienced treatment-related AEs than patients in the atomoxetine or placebo groups (70 [61.4%], 62 [55.4%], and 44 [39.6%], respectively). Fifteen patients experienced AEs that led to discontinuation (guanfacine PR: 9 [7.9%]; atomoxetine: 5 [4.5%]; placebo: 1 [0.9%]). There were no fatal AEs during the study[1].

3.4.2 Pooled safety data

Of the 2411 exposed patients, 1718 were aged 6–12 years and 693 were aged 13–17 years[4]. Mean duration of exposure was 142 days (median 70 days) and 101 patients were exposed for more than 720 days. Rates of treatment-emergent AEs (TEAEs) were higher in guanfacine PR-treated patients as compared to placebo- or atomoxetine-treated patients, in particular regarding severe TEAEs (8.8% versus 1.7% [placebo]/1.8% [atomoxetine], TEAEs related to investigational product (73.2% versus 36.7% (placebo)/55.4% [atomoxetine]), and TEAEs leading to study discontinuation (10.8% versus 1.3% [placebo]/4.5% [atomoxetine])[4].

Similar to other alpha-2 adrenergic medicines, guanfacine PR had cardiovascular effects of bradycardia and hypotension, causing syncope, accidents and injuries[4]. Syncope occurred in 16 (0.7%) guanfacine PR-treated patients (placebo: 0.2%; atomoxetine: 0.0%) and in five healthy volunteers. In addition, a high rate of somnolence and sedation occurred; reported by 50.8% of guanfacine PR-treated patients. There was also the risk of weight gain in particular in the setting of long-term treatment with guanfacine PR[4].

3.5 AWTTC critique

- Medicines licensed for the treatment of ADHD must only be used as part of a comprehensive treatment programme, typically including psychological, educational and social measures. Where pharmacological treatment is indicated, stimulants or non-stimulants may be used. At the time of writing, atomoxetine was the only non-stimulant recommended for use in Wales; guanfacine PR could provide another option for patients requiring treatment with a non-stimulant and also offers a different mechanism of action to atomoxetine.
- There is a lack of direct head to head evidence of guanfacine PR versus atomoxetine. However, study SPD503-316 included atomoxetine as an active reference arm and the effect of guanfacine PR on symptoms was numerically higher than for atomoxetine despite not being powered to test for superiority over atomoxetine[4].
- The company also included a systematic literature review and MTC to address the lack of direct comparative evidence. They conclude that guanfacine PR was consistently numerically favourable compared to atomoxetine, although MTC results should be interpreted with caution due to heterogeneity of the studies with regards to study population, study length and prior treatment.
- In study SPD503-315 and SPD503-316, no consistent effect in adolescents was demonstrated. CHMP noted that these studies were not powered to detect efficacy in the subgroup of adolescents[4]. However, the applicant company provided a variety of plausible reasons for a lack of consistent effect including the small sample size and high placebo response as contributing factors to this result[4]. Furthermore, efficacy was demonstrated in specifically designed adolescent studies considered by CHMP.
- Studies for ADHD medication should demonstrate symptomatic improvement and also alleviate impairment in functioning. In study SPD503-315, the WFRIS-P failed to demonstrate improvement of functioning in ADHD patients, statistically significant results were only observed in SPD503-316. CHMP highlighted a lack of evidence for this effect; however, they noted that methodological assessment of function in psychiatric disorders is a complex and yet unresolved issue, therefore, they did not conclude that guanfacine PR demonstrated a failure in functioning[4].
- CHMP noted that sedation appears not to be well defined in the case of ADHD, where symptomatic improvement and sedation are difficult to distinguish[4]. Whether the effect of guanfacine PR is mediated only through sedation has been a matter of concern for CHMP, also in view of the lack of effect on functioning. However, CHMP add that no clear temporal relationship between

efficacy and reporting of sedation has been demonstrated, suggesting that although contribution of sedation to the reduction on the symptom scale cannot be completely excluded, efficacy may be achieved at least partially via a different mechanism of action[4].

- The most important safety issues associated with guanfacine PR are stated as bradycardia, hypotension, syncope, somnolence and sedation[4]. CHMP highlight that these unfavourable effects are considered to be pharmacologically associated and together constitute the most important risk for the safety of children and adolescents due to risk of accidents and falls causing injury. In addition, they highlight the risk of increased BMI as an important unfavourable effect that may lead to mental and physical health problems in the long term. However, they conclude that appropriate measures including additional pharmacovigilance activities and risk minimisation measures were put in place to help ensure safe and effective use of guanfacine PR within its licensed indication[4].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-utility analysis (CUA) comparing guanfacine PR once daily with atomoxetine once daily, for children and adolescents aged 6–17 years for whom stimulants are not suitable, not tolerated or have been shown to be ineffective[1]. Treatment is assumed to consist of titration (zero to four weeks) and maintenance periods (weeks 5 to 52).

The CUA takes the form of a cohort Markov decision model, which adopts an NHS Wales/Personal Social Services (PSS) perspective, weekly cycles and a time horizon of one year, which negates the need for discounting. Patients enter the model and are exposed to the probabilities of response, non-response, or discontinuation due to AEs. During the titration period even those patients who respond remain at risk of discontinuation until the end of week four. Only patients who are responding to treatment at the end of the titration period are assumed to continue with treatment. Non-responders or those who experience AEs and discontinue treatment by the end of the titration period remain in the non-response state for the remainder of the time horizon.

Efficacy data used to inform the transition probabilities of the model are sourced from the SPD503-316 study[1]. The efficacy difference observed in the study is applied to the titration period and is assumed to remain constant throughout the modelled time horizon.

The medication acquisition costs of guanfacine PR and atomoxetine are calculated as a weighted average, by multiplying the costs per tablet or capsule by the dose distribution of each treatment during the titration and post-titration periods as reported in the SPD503-316 study[1]. The unit cost of guanfacine PR is supplied by the company. Atomoxetine unit costs are sourced from the British National Formulary (BNF)[12]. No administration costs are included, and monitoring costs are captured by the clinical management costs.

Given that a systematic review of the literature reportedly did not identify appropriate data, the resource use associated with the clinical management of patients for each of the health states used in the model is informed by an online survey conducted with 21 UK specialist clinicians whom currently treat children and adolescents with ADHD. Unit costs for these resources have been sourced from NHS reference costs[13] and the PSS Research Unit[14]. AE costs are not included in the analysis. The justification provided for

this is that the only meaningful impact of AEs associated with ADHD treatment is treatment discontinuation, and that AEs dissipate upon treatment discontinuation.

The SPD503-316 study collected health-related quality of life (HRQoL) data using a self-administered, proxy assessed version of the Health Utility Index – Mark 2 and 3. However, the utility data used to inform the base case were taken from a cross-sectional study previously conducted in the UK that recruited 151 children with ADHD with the aim of deriving "*real life*" utility measures using the EuroQol five dimension scale (EQ-5D)[15]. The model assumes that AEs do not impact on HRQoL.

In addition to those already acknowledged, the base case model is characterised by a number of assumptions:

- Patients are transitioned from non-response to response at a constant rate during the four week titration period.
- The rate of discontinuation due to intolerability is the same for responders and non-responders. Also, discontinuations occur during the titration period only.
- The extrapolation applied to the maintenance period is based on an assumption of no changes in health states.
- Non-responders, or those who experience AEs, are assigned the costs and utilities associated with non-response but receive no further active treatment for ADHD.

Probabilistic sensitivity analyses were conducted to test the robustness of the model and account for uncertainties surrounding the utilities and costs associated with the modelled health states. Univariate sensitivity analyses explore the impact of variations in: atomoxetine and guanfacine PR response rates; health state associated utilities; AE related discontinuation; post-titration changes to the percentage of patients receiving 6 mg and 5 mg per day of guanfacine PR; and psychiatrist unit costs. These were further complemented by explorations of variations in: response definitions; titration period and post-titration discontinuation rates; and medical costs associated with health states. Scenario analyses evaluate the effects of using alternative atomoxetine dosing and efficacy inputs.

4.1.2 Results

The results of the base case analysis of the CUA are present in Table 3.

Table 3. Results of the base case analysis.

	Guanfacine PR	Atomoxetine	Difference
Total costs	£2,721.54	£2,639.25	**£82.28**
Total QALYs	0.821	0.815	**0.006**
ICER (£/QALY gained)	**£13,492**		
ICER: incremental cost effectiveness ratio; PR: prolonged-release; QALY: quality-adjusted life-year.			

The results of the univariate sensitivity analyses indicate that the incremental cost effectiveness ratio (ICER) is most sensitive to variations in: the atomoxetine response rate, response utility score, non-response utility score, and the guanfacine PR response rate. Notably, the ICER is highly sensitive to treatment response rates. If the response rate of atomoxetine is increased from the base case of 69.6% to 78.2%, this results in an ICER of £161,177. Similarly, if the response rate of guanfacine PR is reduced from the base case of 82.1% to 75%, this results in an ICER of £59,458.

Probabilistic sensitivity analyses reveal that at willingness-to-pay thresholds of £20,000 and £30,000 per quality-adjusted life-year (QALY) gained, guanfacine PR has a 52.6% and 61.1% chance of being the most cost-effective treatment option respectively. The simulation data reveals that approximately 79% of the ICER estimates fall within the

northeast (NE) quadrant of the cost-effectiveness plane (i.e. additional costs for QALY gains); 14% fall in the northwest (NW) quadrant (additional costs for QALYs lost: guanfacine PR is dominated); 5% fall in the southeast (SE) quadrant (costs saved for QALYs gained: guanfacine PR dominates), and 1% fall in the southwest (SW) quadrant (costs saved for QALYs lost).

Table 4. Summary of results for the scenario analyses conducted.

Scenarios	ICER	Probability of being cost effective		Plausibility
		WTP £20,000	WTP £30,000	
10% of atomoxetine patients receiving twice daily dosing	**£4,985**	67.4%	71.8%	The SPC for atomoxetine states that some patients may require twice daily dosing[11].
MTC efficacy inputs	**£27,670**	37.3%	43.4%	Given that the study underpinning the economic model was not powered to detect differences between guanfacine PR and atomoxetine, this is a plausible scenario; albeit also limited in view of it being based on indirect treatment comparisons.
MTC efficacy inputs assuming 10% atomoxetine twice daily dosing	**£12,982**	48.4%	52.4%	This scenario combines the two scenarios above; and as such is subject to the same limitations and strengths.
ICER: incremental cost-effectiveness ratio; MTC: mixed treatment comparison; PR: prolonged-release; SPC: summary of product characteristics; WTP: willingness-to-pay threshold.				

4.1.3 AWTTC critique

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the base case analysis.
- A variety of scenarios and sensitivity analyses have been considered to test the robustness of the base case results.

Limitations:

- The SPD503-316 study was powered to detect a statistical difference between guanfacine PR and placebo, but not between guanfacine PR and atomoxetine (which was included as a reference comparator). Also, just two of the 338 study participants were based in the UK. This introduces uncertainty in terms of the robustness of the data which underpins the model, and the potential for generalisability to the Welsh context.
- Treatment response is considered to have been achieved if a patient's ADHD-RS-IV score is reduced by 30% or more from baseline. However, when titrating treatment with an aim to achieve optimal efficacy the company combine this measure with a CGI-I of 1 or 2 to measure response. If the definition of response is changed in the model to reflect this combination, this increases the base case ICER to £16,666.
- The analyses revealed a high degree of ICER sensitivity related to the response rates for guanfacine PR and atomoxetine. Using the confidence intervals from the SPD503-316 study to guide sensitivity analyses resulted in ICERs significantly higher than the base case.
- Whilst the modelled four week titration period is reflective of current practice for 6–12 year olds, this period sometimes increases to seven weeks for 13–17 year olds (depending on their weight)[2]. This extended titration period was reflected in the SPD503-316 study design. The discrepancy between actual and modelled titration periods potentially has implications for discontinuation rates and the ICER generated by the model.

- The longer term assumption of a fixed response rate and no discontinuation during the maintenance phase may over-simplify the model. In practice monitoring continues for the first year, and discontinuation remains a possibility during this period[2]. The company has, however, sought to address this via sensitivity analyses.
- The one year time horizon adopted may be insufficient if treatment and outcomes are likely to continue beyond this point.
- Discontinuation due to AEs is assumed to have the same impact on resource use and HRQoL as non-response.
- The health state utility scores used in the base case were not taken from the SPD503-316 study. However, application of the SPD503-316 utility scores within the model generates an ICER of £27,853 which introduces uncertainty around the QALY estimates.
- Whilst the sensitivity analyses explore the impact of twice daily dosing of atomoxetine in terms of costs, there is no consideration of how this may influence the effectiveness of atomoxetine.
- The results of the univariate sensitivity analyses have not been fully explored in the submission in terms of plausibility. This would have been beneficial given the magnitude of the ICER generated in relation to the variation in atomoxetine and guanfacine PR response rates.
- The resource use estimates provided by the clinical experts introduce uncertainty and the potential for bias. Just one of the 21 UK based clinicians currently practices in Wales.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) identified a number of relevant evaluations, predominantly in the form of conference papers. The most recent conference paper[16], and the only one with a UK focus, was also based on data from the SPD503-316 study. The reported ICER was £2,303/QALY gained when guanfacine PR was compared with atomoxetine. Notably, in contrast to the submission, this evaluation used the health state utility values collected in the study. The probability of the ICER falling below a willingness-to-pay threshold of £20,000 was estimated as being 76.1%. All of the other evaluations identified have an international focus, and are therefore limited in their applicability to the Welsh setting. One publication comparing guanfacine PR and atomoxetine in the Canadian context reported an associated 0.007 QALY gain[17]. This can be contrasted with a QALY gain of 0.006 in the base case submission, and a 0.003 QALY gain when mean utility scores from the SPD503-316 study are used in the submitted model.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Given the lack of data on ADHD prevalence in Wales, the company has estimated there to be 3,511 children and adolescents with ADHD in Wales. This figure has been estimated using Welsh population data[18] combined with prevalence data for the whole of the UK[19]. It is assumed that there are no changes over time in the total population size, and the predicted prevalence remains constant in the budget impact analyses calculations. According to company estimates the market share for non-stimulants is 10%[1]. The company predict that the uptake of guanfacine PR will increase from 11% to 61% over a five year period. The medication costs included in the model represent the post-titration costs only. The number of patients treated with atomoxetine in each year is multiplied by the cost difference per patient per annum to calculate the corresponding budget impact. Sensitivity analyses explore how the budget model responds to changes in the following parameters: the acquisition cost of guanfacine PR

and atomoxetine; the proportion of patients prescribed non-stimulants (i.e. varying the eligible population); and the uptake rate of guanfacine PR.

5.1.2 Results

The budget impact analyses reveal increased costs associated with medicine acquisition for this patient group by the introduction of guanfacine PR. Table 5 details the projected net cost per annum, and cumulative net costs. Table 6 summarises the results of the sensitivity analyses.

Table 5. Company-reported costs associated with use of guanfacine PR for the indication covered in this submission[1].

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Number of eligible patients	351	351	351	351	351
Uptake of guanfacine PR (%)	11%	24%	39%	56%	61%
Number of patients treated with guanfacine PR	**39**	**84**	**137**	**197**	**214**
Number of patients treated with atomoxetine	312	267	214	154	137
Net costs					
Guanfacine PR cost per patient per annum	£1,045.97	£1,045.97	£1,045.97	£1,045.97	£1,045.97
Atomoxetine cost per patient per annum	£837.16	£837.16	£837.16	£837.16	£837.16
Cost difference per patient per annum	£208.81	£208.81	£208.81	£208.81	£208.81
Overall net cost	**£8,143.59**	**£17,540.04**	**£28,606.97**	**£41,135.57**	**£44,685.34**
Cumulative net cost	**£8,143.59**	**£25,683.63**	**£54,290.60**	**£95,426.17**	**£140,111.51**

PR: prolonged-release.

Table 6. Scenario analyses of budget impact parameters[1].

Scenario		Incremental cost of guanfacine PR per annum					
		Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)	Total
Cost of guanfacine PR	+20%	£16,144	£35,223	£57,237	£82,186	£89,524	£280,314
	−20%	−£15	−£32	−£53	−£76	−£82	−£258
Cost of atomoxetine	+20%	£1,598	£3,487	£5,666	£8,136	£8,862	£27,748
	−20%	£14,531	£31,704	£51,518	£73,975	£80,580	£252,308
ADHD non-stimulant population	+20%	£9,677	£21,114	£34,311	£49,266	£53,665	£168,034
	−20%	£6,452	£14,076	£22,874	£32,844	£35,777	£112,023
Uptake rate of new technology	+20%	£9,677	£21,114	£34,311	£49,266	£53,665	£168,034
	−20%	£6,452	£14,076	£22,874	£32,844	£35,777	£112,023

ADHD: attention deficit hyperactivity disorder; PR: prolonged-release.

5.1.3 AWTTC critique

The budget impact analyses are characterised by both strengths and limitations, the most salient of which are detailed below:

- The submission gives a detailed, transparent account of the methods and data sources used in the budget impact analysis.
- The UK prevalence of ADHD in this patient group is sourced from a survey conducted in 1999. It is uncertain if this prevalence has remained unchanged in the UK since the time of survey and whether or not Wales has the same prevalence as that of the UK as a whole.

- The sensitivity analyses conducted are possibly overly simplistic in assigning ±20% variations to the parameters of interest. However, this is often considered an acceptable approach when there is uncertainty surrounding plausible parameters.

5.2 Comparative unit costs

Comparative unit costs are provided in Table 7.

Table 7. Examples of medicine acquisition costs for non-stimulant ADHD treatments.

Regimens	Example doses	Approximate costs per patient (per annum)
Guanfacine PR (Intuniv®▼)	1–7 mg once daily*	£731–£1848
Atomoxetine (Strattera®)	25–120 mg once daily**	£815–£1630

See relevant Summaries of Product Characteristics for full licensed indications and dosing details[2,11].
Costs are based on the British National Formulary list prices as of December 2015[12] or company estimated.
Costs of administration are not included.
This table does not imply therapeutic equivalence of medicines or the stated doses.

*The recommended starting dose is 1 mg and up to 7 mg of guanfacine can be used for adolescents weighing at least 58.5 kg.
**The usual maintenance dose for children and adolescents aged 6–17 (body-weight up to 70 kg) is 1.2 mg/kg of atomoxetine daily. The average weight of a six year old child is approximately 20 kg; this has been used to guide the lower estimate. Maximum maintenance dose for atomoxetine is 120 mg daily.

PR: prolonged-release.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, guanfacine (Intuniv®▼) may be appropriate for prescribing within NHS Wales for the indication under consideration with a shared care agreement.

The company do not anticipate that guanfacine (Intuniv®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 3 December 2015.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

ADHD Rating Scale IV (ADHD-RS-IV)[20]

ADHD-RS-IV is a questionnaire used to both diagnose ADHD in children and adolescents and assess treatment response. The scale consists of two subscales: inattention (nine items) and hyperactivity-impulsivity (nine items), and is linked directly to DSM–IV diagnostic criteria for ADHD. The questionnaire is completed independently by the parent and/or teacher and scored by a clinician. Higher scores indicate increased inattention or hyperactivity-impulsivity.

Clinical Global Impressions (CGI) scale[21]

The CGI scale was developed for use in National Institute of Mental Health (NIMH)-sponsored clinical trials to provide a brief, standalone clinician assessment of a patient's global functioning prior to and after initiating study medication. It provides an overall summary measure that takes into account all available information (patient history, symptoms, behaviour etc) and is applicable to all psychiatric conditions. The CGI scale comprises two, one-item measures:

- **Clinical Global Impressions - Severity (CGI-S)**
  A seven-point scale of severity in which, in assessing a patient, the clinician asks him or herself one question: Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? A higher score indicates more severe illness.
- **Clinical Global Impressions – Improvement (CGI-I)**
  A seven-point scale of the change from baseline in which, in assessing a patient, the clinician asks him or herself one question: Compared to the patient's condition prior to medication initiation, this patient's condition is: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse?

Treatment failure[1]

Treatment failure was defined as ≥ 50% increase (worsening) in ADHD-RS-IV total score and a ≥ 2 point increase (worsening) in CGI-S score compared with the respective scores at the double-blind randomised-withdrawal baseline visit (visit 13/week 13) at two consecutive double-blind randomised-withdrawal phase visits. All patients who discontinued the study for any reason were regarded as treatment failures for the primary analysis.

Weiss Functional Impairment Rating Scale-Parent (WFIRS-P)[10,22]

The WFIRS-P questionnaire comprises 50 items grouped into six domains and addresses the domains of daily functioning that are likely to be impaired in ADHD. The items relate to the past month and are scored using a 4-point Likert scale: 0 (never or not at all); 1 (sometimes or somewhat); 2 (often or much); or 3 (very often or very much). Higher WFIRS-P scores indicate more severe functional impairment.

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