New Medicine Recommendation

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

For treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

Recommendation: Amber level 1 (with shared care)

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Minimal monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Full prior agreement about patient's on-going care must be reached under the shared care agreement.

Primary care prescribers are advised not to take on prescribing of these medicines unless they have been adequately informed by letter of their responsibilities with regards monitoring, side effects and interactions and are happy to take on the prescribing responsibility. A copy of locally approved shared care guidelines should accompany this letter which outlines these responsibilities. Primary care prescribers should then tell secondary care of their intentions as soon as possible by letter so that arrangements can be made for the transfer of care.

Supporting statement:

The SMC accepted guanfacine for use within NHS Scotland for 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. Treatment must be used as part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures.[1]

Details of Review

Name of medicine: Guanfacine (Intuniv®)
Strengths and form: 1 mg, 2 mg, 3 mg, 4 mg prolonged-release tablets [2]
Dose and administration: 4mg to 7mg daily (maintenance dose)
BNF therapeutic class / mode of action: 4.4 CNS stimulants and other drugs for attention deficit hyperactivity disorder
Licensed indication: Guanfacine (Intuniv®) is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Intuniv® must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures.[2]
Proposed use: As above
Course and cost: 1mg tab, 28=£56.00. 2mg tab, 28=£58.52. 3mg tab, 28=£65.52. 4mg tab, 28=£76.16.[3] For all patients, 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 1mg per week. Dose should be individualised according to the patient's response and tolerability. The maximum dose is 7mg each day.[2] The standard dose titration in the lowest weight group is to 4mg per day which will cost £990.08 for one year's treatment. At the maximum weight/dosage of 7mg daily, one year's treatment will cost £1841.84 (excluding VAT)
Current standard of care/comparator therapies: Atomoxetine capsules (Strattera®) cost £62.46–£83.28 for 28 days treatment at a dose of 10–100 mg daily (excluding VAT) Atomoxetine 4 mg/ml oral solution (Strattera®) costs £23.33–£233.33 for 28 days treatment at a dose of 10–100mg daily (excluding VAT)[4] Clonidine (not licensed in this indication), the SMC quote a dose range of 50 to 300micrograms orally once daily, dependent on age and weight. 28 days treatment will cost between £4.58 and £6.75 (excluding VAT)[5]
Relevant NICE guidance: The National Institute for Health and Care Excellence (NICE) produced clinical guideline 72, 'Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults', in September 2008 (last modified February 2016). The guideline advises that pharmacological treatment of ADHD in school-age children and adolescents is indicated first line in severe forms of the condition. Where drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are the recommended options, within their licensed indications. Generally, atomoxetine should be considered if methylphenidate has been tried but is ineffective at the maximum tolerated dose, or if the child or adolescent is intolerant to low or moderate doses of methylphenidate. Dexamfetamine should be considered in children and adolescents whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine. Pharmacological treatment for ADHD should be continued for as long as it is

clinically effective and reviewed at least annually.[6]

NICE produced an evidence summary for guanfacine ESNM70 in March 2016 which is not NICE guidance; it aims to provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The summary states:

- In 1 short-term RCT, dose-optimised guanfacine prolonged-release was more effective than placebo at improving ADHD symptoms in children and young people aged 6–17 years (about half of whom had previously been treated with stimulant medication; p<0.001, effect size=0.76; n=338).
- In 2 other short-term RCTs, dose-optimised guanfacine prolonged-release was more effective than placebo at improving ADHD symptoms in young people aged 13–17 years (p<0.001, effect size=0.52; n=314) and in children aged 6–12 years (p<0.001; n=333)[7]

Disease Background

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous neurobehavioural disorder and one of the most common neurodevelopmental disorders in children. The condition is characterised by symptoms of inattention, hyperactivity, impulsivity and impairment of executive functions.

Treatment of ADHD aims to improve attention, reduce hyperactivity/impulsivity and improve the associated behavioural and relational problems. Improvement in the symptoms of ADHD is considered to be an important step in the management of the condition. [8]

Current UK guidelines recommend a psychostimulant as first-line treatment. Atomoxetine, a non-stimulant, is recommended when stimulants are not appropriate, not tolerated, ineffective, or where there is a risk of misuse.[9 10 11]

Guanfacine is a selective alpha2A-adrenergic receptor agonist and a non-stimulant. Its mode of action in ADHD has not been fully established, though it is thought to exert its effect through modulation of signalling in the prefrontal cortex and basal ganglia by directly modifying transmission of synaptic noradrenaline at the alpha2-adrenergic receptors.[2 8]

Summary of evidence

Clinical evidence derives from two key studies, SPD503-316 and SPD503-315. Study SPD503-316 was a phase III, randomised, double-blind, placebo-controlled study which assessed the efficacy and safety of guanfacine prolonged-release tablets compared with placebo in children and adolescents aged 6 to 17 years old with ADHD of at least moderate severity. The study excluded patients with a co-morbid psychiatric diagnosis (other than oppositional defiant disorder [ODD]).

Patients were randomised equally to guanfacine prolonged-release tablets (n=114), atomoxetine capsules (n=112) or placebo (n=111). Randomisation was stratified by age group (children aged 6 to 12 years or adolescents aged 13 to 17 years) and by country. Atomoxetine was only included as a reference arm to provide data against placebo.[12]

Study drugs were administered in a double-dummy design, taken once daily each morning. Patients entered a double-blind dose-optimisation phase, followed by a six-week double-blind maintenance phase and a two-week double-blind dose tapering phase. Guanfacine was initiated at 1mg/day and increased by weekly 1mg increments to a maximum of 4mg/day in children, or a maximum of 4 to 7mg/day in adolescents. Atomoxetine was titrated to a target of 1.2mg/kg/day (maximum 1.4mg/kg/day) in patients weighing <70kg, or to a maximum of 100mg/day in patients weighing ≥70kg. In the guanfacine, atomoxetine

and placebo groups, respectively, prior use of at least one stimulant medicine was reported by 47% (54/114), 51% (57/112) and 50% (56/111) of patients. The primary outcome was the change from baseline in the investigator-rated ADHD-RS-IV total score at week 10 for children and week 13 for adolescents. Patients treated with guanfacine had a significantly greater reduction in the ADHD-RS-IV total score compared with placebo from baseline to week 10/13.[12] Results are presented in table 1.

Table 1: Primary outcome analyses of the ADHD-RS-IV total scores[3]

	Guanfacine (n=114)	Atomoxetine (n=112)	Placebo (n=111)
Baseline mean (SD) score	43.1 (5.47)	43.7 (5.86)	43.2 (5.60)
Mean (SD) score at week 10/13	19.2 (11.85)	25.0 (12.97)	28.1 (14.13)
Mean (SD) change in score from baseline to week 10/13	-23.9 (12.41)	-18.6 (11.91)	-15.0 (13.07)
LS mean (SE) change in score	-23.9 (1.2)	-18.8 (1.2)	-15.0 (1.2)
Difference in LS mean compared with placebo (95% CI)	-8.9 (-11.9 to -5.8)	-3.8 (-6.8 to -0.7)	N/A
Effect size	0.76	0.32	N/A
p-value versus placebo	<0.001	0.017 (nominal)	N/A

ADHD-RS-IV=attention deficit hyperactivity disorder rating scale IV; Effect size was calculated as the absolute difference in least squares means between active treatment and placebo divided by the root mean square error; SD=standard deviation; LS=least squares; SE=standard error; CI=confidence interval; N/A=not applicable

The primary analysis methodology was used for a comparison between guanfacine and atomoxetine reference arm in a pre-specified secondary outcome analysis that was not controlled for multiplicity. Patients treated with guanfacine had a nominally significantly greater reduction in ADHD-RS-IV total score compared with atomoxetine from baseline to week 10/13, with a least squares mean difference in scores of -5.1 (95% confidence interval [CI]: -8.2 to -2.0), nominal p=0.001, effect size 0.440.[3]

The key secondary outcomes, assessed from baseline to week 10/13, were the CGI-I score and disease-specific function. Guanfacine was significantly superior to placebo for these key secondary outcomes.[12] Results are presented in table 2

Table 2: Secondary outcome analyses (baseline to week 10/13) of the CGI-I scores and WFIRS-P domains[3]

	Guanfacine (n=114)	Atomoxetine (n=112)	Placebo (n=111)
CGI-I score			
Proportion of patients rated as 'improved' (score of 1 or 2) at week 10/13 % (n/N)	68% (76/114)	56% (63/112)	44% (49/111)
Difference in % improvement compared with placebo (95% CI)	24% (11.1 to 36.4)	12% (-0.9 to 25.1)	N/A
p-value versus placebo	<0.001	0.024 (nominal)	N/A
WFIRS-P learning and school domain			
Difference in LS mean compared with placebo (95% CI)	-0.22 (-0.36 to -0.08)	-0.16 (-0.31 to -0.02)	N/A
Effect size	0.42	0.32	N/A
p-value versus placebo	0.003	0.026 (nominal)	N/A
WFIRS-P family domain			
Difference in LS mean compared with placebo (95% CI)	-0.21 (-0.36 to -0.06)	-0.09 (-0.24 to -0.06)	N/A
Effect size	0.38	0.16	N/A
p-value versus placebo	0.006	0.242 (nominal)	N/A

CGI-I=Clinical Global Impression-Improvement; WFIRS-P=Weiss Functional Impairment Rating Scale-Parent Report; Effect size was calculated as the absolute difference in least squares means between active treatment and placebo divided by the root mean square error; CI=confidence interval; N/A=not applicable; LS=least squares

CGI-S was also assessed as a secondary outcome, and by week 10/13, a significantly greater proportion of patients in the guanfacine group had a normal/borderline CGI-S rating compared with placebo; difference 12% (95% CI: 0.2 to 24.3), p=0.04.[12 13]

An ad-hoc analysis of time to onset of efficacy for the ADHD-RS-IV total score was also performed (ie time to when the first statistical difference between guanfacine and placebo occurred); a significant difference between guanfacine and placebo was observed from week one, with a least squares mean difference in scores of -2.6 (95% CI: -4.3 to -0.9), p=0.003, effect size 0.40.[12]

Study SPD503-315 was a phase III, double-blind, placebo-controlled, randomised-withdrawal study which assessed the long-term maintenance of efficacy and safety of guanfacine prolonged-release tablets compared with placebo in children and adolescents aged 6 to 17 years old with ADHD. The inclusion and exclusion criteria, response criteria, guanfacine titration and maximum dosing per age group matched study SPD503-316. All patients were allocated to treatment with guanfacine (n=528) in a 13-week open-label phase which was completed by 60% (316/528) of patients.

Patients then entered a 26-week double-blind randomised-withdrawal phase and were randomly allocated to continue with guanfacine prolonged-release tablets (n=157) or switch to placebo (n=159). There was a high drop-out rate in both groups, with only 48% (76/157) and 33% (53/159) of patients in the guanfacine and placebo groups, respectively, completing the study.[14 15]
The primary outcome was the percentage of patients with treatment failures during the double blind randomised-withdrawal phase from baseline (week 13) to week 26. Treatment failure was defined as a ≥50% increase (worsening) in ADHD-RS-IV total score and a ≥2 point increase (worsening) in CGI-S score for two consecutive visits compared with baseline. A significantly smaller proportion of patients treated with guanfacine (49% [74/150]); 95% CI: 41 to 57) were classed as treatment failures during this phase compared with placebo (65% [98/151]; 95% CI: 57 to 72); treatment difference -16% (95% CI: -27 to -4.5), p=0.006.[8]

The key secondary outcome was the time to treatment failure during the double-blind

randomised-withdrawal phase (week 13 to week 26). Patients in the guanfacine group had a significantly longer time to treatment failure (median 218 days; 95% CI: not reported) compared with the placebo group (median 56 days; 95% CI: 44 to 97); p=0.003.

Nominally significant differences were also demonstrated for secondary outcome analyses (week 13 to 26) for guanfacine versus placebo for change in ADHD-RS-IV total score and percentage of patients with an assessment of normal/borderline mentally ill on the CGI-S scale; there was no significant difference for the change in the WFIRS-P global score.[14]

Supportive evidence was presented from a number of phase III, double-blind, randomised, placebo-controlled studies which assessed the efficacy and safety of guanfacine prolonged release tablets compared with placebo in children and adolescents aged 6 to 17 years old diagnosed with ADHD. Change in ADHD-RS-IV total score was assessed as a primary outcome in studies SPD503-301, SPD503-304 and SPD503-313 which compared guanfacine with placebo, and as a secondary outcome in the long-term guanfacine monotherapy extension studies SPD503-303 and SPD503-305; these studies demonstrated that patients treated with guanfacine achieved significant reductions in the ADHD-RS-IV total score. Significant improvements were also demonstrated for secondary outcome analyses of the studies reporting CG-I, Parent's Global Assessment (PGA), Conners' Parent Rating Scale–Revised: Short Form (CPRSR) and Child Health Questionnaire-Parent Form 50 (CHQ-PF50).[16 17 18 19 20]

Summary of safety data:

In the guanfacine, atomoxetine and placebo groups of study SPD503-316, respectively, treatment-emergent adverse events were reported in 77% (88/114), 68% (76/112) and 66% (73/111) of patients, in which 7.0%, 1.8% and 2.7% were considered to be severe. Serious treatment-related adverse events were reported in one patient (0.9%) in each of the guanfacine and placebo groups. Treatment discontinuation as a result of adverse events occurred in 7.9% (9/114), 4.5% (5/112) and 0.9% (1/111) of patients in the guanfacine, atomoxetine and placebo groups, respectively.[12]

The European Public Assessment Report (EPAR) for guanfacine considered that these differences between treatment groups were substantial and questioned the tolerability of guanfacine compared with alternative treatments.[8] The most commonly reported adverse events in the guanfacine group were somnolence (44% [50/114], versus 18% [20/112] in the atomoxetine group and 14% [16/111] in the placebo group), headache (26% [30/114] versus 20% [22/112] and 24% [27/111]), and fatigue (25% [29/114] versus 21% [24/112] and 18% [20/111]).[12]

The EPAR noted that across all studies, adverse effects such as orthostatic hypotension, bradycardia, hypno-sedation, fatigue and headache were very common and could limit tolerability. Rebound hypertension and tachycardia may also occur after discontinuation of guanfacine, particularly if abrupt. The scientific advisory group on psychiatry considered safety to be of concern with guanfacine with regards to sedation, cardiovascular effects and obesity, however despite the identified safety risks and uncertainties for guanfacine, the safety profile was considered to be acceptable. A long-term comparative post-authorisation safety study is to be conducted.[8]

Strengths and limitations of the evidence:

Strengths:

- The studies demonstrated that guanfacine significantly improved ADHD symptoms and functional outcomes compared with placebo, but no data were presented versus an active comparator
- Only patients with ADHD of at least moderate severity were included in the key

study populations. This is consistent with Scottish practice and the NICE guideline where pharmacological treatment is recommended in patients with moderate to severe ADHD. [9] [11]

- The majority of patients were males aged 6 to 12 years old and ADHD is known to be more prevalent in males.
- Initial concerns with guanfacine regarding a lack of efficacy in adolescents, the possibility of symptom correction being predominantly due to sedation, and a lack of effect on functioning were raised in the EPAR. These concerns were subsequently considered to be addressed satisfactorily during the assessment process and the symptomatic effect of guanfacine was considered to be clinically meaningful.[8]

Limitations:

- Atomoxetine was only included as a reference arm in study SPD503-316, and although guanfacine was found to be numerically superior to atomoxetine in a pre-specified secondary outcome analysis, the result was only nominally significant as no adjustments were made for multiplicity.
- There was a high drop-out rate in study SPD503-315; the EPAR commented that the high rate of withdrawal from long-term studies created doubt over adherence in clinical practice, although data from studies SPD503-303 and SPD503-305 suggested that efficacy was maintained in those patients continuing with treatment in the long term.
- Patients with a co-morbid psychiatric diagnosis (except ODD) were excluded from the studies which may affect the generalisability of the results to the patient population.

Summary of evidence on cost effectiveness:

The clinical efficacy data used to support the economic analysis were taken from a Health Technology Assessment statistical analysis report which supported the SPD503-316 study. Based on the pre-specified analysis of ADHD responder definitions, guanfacine had a response rate of 82% compared to 70% for atomoxetine. However, atomoxetine was included as a reference comparator only and the study was not powered to detect a statistically significant difference between guanfacine and atomoxetine. The company conducted a network meta-analysis (NMA) and the results of this analysis were provided in the sensitivity analysis. The results of the NMA indicated that guanfacine resulted in a higher response rate versus atomoxetine (55.9% vs. 49.7% respectively) but these results were not statistically significant, as the confidence intervals overlapped.

The submitting company presented results of Bayesian network meta-analyses as the data source for a sensitivity analysis in the economic model. The NMA compared guanfacine prolonged-release tablets with lisdexamfetamine dimesylate, atomoxetine, methylphenidate extended-release and methylphenidate immediate-release. Change in the ADHD-RS-IV score and CGI-I response were reported as efficacy outcomes. Safety outcomes were all cause discontinuation and discontinuation due to adverse events. The key comparison was guanfacine versus atomoxetine; 95% credible intervals for the efficacy and safety outcomes overlapped, suggesting that the treatments were similar. The results of the NMA were limited by heterogeneity in study population and design, and lack of clarity in terms of the studies included. In addition, the target population did not specifically include patients for whom stimulants were not suitable, not tolerated or shown to be ineffective, limiting its generalisability.

Based on the numerical differences in efficacy from this analysis, guanfacine resulted in an ICER of £27,573, based on an incremental cost of £72 and an incremental QALY gain of 0.003. The results of a Cost Minimisation Analysis performed by the SMC showed that guanfacine would not be cost-minimising, and instead be associated with a small

incremental cost per patient per year of between £131 and £149. This was reduced to an additional cost of £90- £103 per year if bi-daily atomoxetine dosing was assumed.

A conservative additional analysis whereby discontinuation rates are applied to both treatment arms in the post- titration phase (discontinuation rate assumed to reflect the titration phase i.e. 7.9% and 4.5% for guanfacine and atomoxetine respectively) was conducted. In this analysis, the ICER increased to £26,350 compared to atomoxetine, based on an incremental cost of £89 and an incremental QALY gain of 0.003, but it should be noted that if the majority of discontinuation occurs in the titration phase, then this figure will overstate the ICER.

Prescribing and risk management issues:

There are pre-treatment screening and monitoring requirements for somnolence and sedation, cardiovascular status, heart rate, blood pressure, height, weight and body mass index. Somnolence and sedation can occur mainly at the start of treatment, typically lasting for 2–3 weeks and longer in some cases. Undesirable side effects are common and limit tolerability.[7]

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per year
Guanfacine	4 to 7mg daily	£76.16 to £141.68	£990 to £1842
Atomoxetine	10 to 100mg orally in one or two divided doses	£62.46 to £83.28	£812 to £1083
Clonidine	50 to 300micrograms orally once daily	£3.46 to £6.77	£45 to £88
Costs based on MIMS list prices April 2016, excluding VAT. Table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

N/A

Productivity, service delivery, implementation:

If used for over 12 months, the usefulness of guanfacine should be re-evaluated every three months for the first year and then at least yearly based on clinical judgement. Trial periods off medication should be considered to assess the patient's functioning. Patients/caregivers should be instructed not to discontinue guanfacine without consulting their physician.

Tapering the dosing during withdrawal is recommended to minimise potential withdrawal effects.

Anticipated patient numbers and net budget impact:

The number of patients estimated to be eligible for treatment was 574 in all years, with an estimated uptake rate of 10% in year 1, rising to 50% in year 5. The gross medicines budget impact in year 1 was estimated to be £60k, rising to £300k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was assumed

to be £12k in year 1, rising to £60k in year 5. It should be noted that the estimated number of eligible patients appear to have been underestimated by the company, therefore the budget impact may be higher.

Scotland has a population of 5,295,000[21] therefore the incidence per 100, 000 population can be calculated to be 10.8 per 100, 000 population. For Lancashire, with a population of around 1.5 million, the incidence is expected to be 163 patients.

For 10% in the first year, Lancashire would expect to treat around 16 patients costing around £24, 000 and by year five around 82 patients costing around £123, 000. These figures are roughly in line with NICE ESNM70.[7]

Innovation, need, equity:

Guanfacine would provide an alternative licensed non-stimulant treatment option for the management of ADHD in children and adolescents, with a different mechanism of action to the existing licensed treatments. Clinical experts consulted by SMC consider there is unmet need in this therapeutic area for patients who do not respond to existing treatments, and regard guanfacine as a therapeutic advancement with a better safety profile than clonidine.

Having an additional medication option in the form of guanfacine would be very beneficial to children with ADHD, particularly those who cannot tolerate the stimulant medications. Effective medication for ADHD can make a huge difference to children and their families.

References

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