

guanfacine, 1mg, 2mg, 3mg and 4mg prolonged-release tablets (Intuniv[®])
SMC No. (1123/16)

Shire Pharmaceutical Contracts Ltd

8 January 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

guanfacine (Intuniv[®]) is accepted for use within NHS Scotland.

Indication under review: 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.

Two phase III studies in children and adolescents aged 6 to 17 years with ADHD demonstrated that guanfacine improved the symptoms of ADHD compared with placebo.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

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.

Dosing Information

Treatment must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders. The recommended starting dose is 1mg guanfacine orally, swallowed whole, once a day in the morning or evening. The dose may be adjusted in increments of not more than 1mg per week and should be individualised according to the patient's response and tolerability. The recommended maintenance dose range is 0.05 to 0.12mg/kg/day. The recommended dose titration for children and adolescents is provided in the summary of product characteristics.

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.

Product availability date

December 2015

Summary of evidence on comparative efficacy

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. Guanfacine is a selective α_{2A} -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 α_2 -adrenergic receptors.^{1,2} Atomoxetine is currently the only licensed non-stimulant treatment for ADHD in children and adolescents accepted for use in NHS Scotland.

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 (ie baseline ADHD rating scale IV [ADHD-RS-IV] total score ≥ 32 and Clinical Global Impression-Severity of illness [CGI-S] score ≥ 4). Patients had age-appropriate intellectual functioning and blood pressure measurements within the 95th percentile for age, sex and height. 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.³

Study drugs were administered in a double-dummy design, taken once daily each morning. Patients entered a double-blind dose-optimisation phase (four weeks for children and seven weeks for adolescents to allow for weekly dose titration), 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 (dose determined by weight). 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. Criteria for dose titration were based on optimal treatment response which was defined as a ≥30% reduction in the ADHD-RS-IV total score from baseline and a CGI-Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved), with no associated safety or tolerability problems. 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 10/13.³ Results are presented in table 1.

Table 1: Primary outcome analyses of the ADHD-RS-IV total scores³

| | 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 (assessed by a change in Weiss Functional Impairment Rating Scale-Parent Report [WFIRS-P] learning and school domain, and family domain). Guanfacine was

significantly superior to placebo for these key secondary outcomes.³ Results are presented in table 2.

Table 2: Secondary outcome analyses (baseline to week 10/13) of the CGI-I scores and WFIRS-P domains³

| | 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), $p=0.04$.^{3,4} 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 0.40.³

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.^{6,7}

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 $\geq 50\%$ 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 during the 26-week phase. 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), $p=0.006$.² 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. Similar health utilities index-2/3 scores were observed for both the guanfacine and placebo groups.⁶

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 (CPRS-R) and Child Health Questionnaire-Parent Form 50 (CHQ-PF50).^{8,9,10,11,12}

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

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.³ 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.² 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]).³

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.²

Summary of clinical effectiveness issues

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.² 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.^{13,14,15} Clinical experts consulted by SMC considered that atomoxetine and clonidine are the non-stimulant treatment options for ADHD in children and adolescents. Clonidine is not licensed in the UK for the treatment of ADHD.

The studies demonstrated that guanfacine significantly improved ADHD symptoms and functional outcomes compared with placebo, but no data were presented versus an active comparator. 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 Scottish population. Only patients with ADHD of at least moderate severity were included in the key study populations. However, this is consistent with Scottish practice where pharmacological treatment is recommended in patients with moderate to severe ADHD.¹³ The majority of patients were males aged 6 to 12 years old and ADHD is known to be more prevalent in males. There was no requirement to recruit patients for whom stimulants were not suitable, not tolerated or shown to be ineffective, in line with the licensed indication for guanfacine, however prior stimulant use was reported in 47% of patients in study SPD503-316. 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.^{2,13}

The submitting company presented results of Bayesian network meta-analyses (NMA) 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.

Guanfacine is a known antihypertensive which reduces peripheral vascular resistance, blood pressure and heart rate. The summary of product characteristics advises that prior to prescribing there should be baseline evaluations of blood pressure and heart rate, history of concomitant medications, previous and current co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and recording of pre-treatment height and weight. Monitoring for signs and symptoms of somnolence, sedation, hypotension and bradycardia should be performed weekly during dose titration. Patients should then be assessed at least every three months during the first year of treatment, and six-monthly thereafter. More frequent monitoring is advised following any dose adjustment or when discontinuing treatment.¹

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.

Other data were also assessed but remain commercially confidential.*

Summary of comparative health economic evidence

The company provided a cost-utility analysis comparing guanfacine to atomoxetine for the treatment of ADHD in children and adolescents aged 6-17 years for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. A Markov model, consisting of nested decision trees was submitted and comprised of two health states i.e. response and non-response. The definition of each health state was based on the ADHD-RS-IV score of each patient. Patients considered to be responders were those with a reduction in ADHD-RS-IV score of >30% from baseline while patients considered to be non-responders were those with a reduction in ADHD-RS-IV score of <30% from baseline. Transition probabilities were used within the model to estimate the likelihood of patient response to treatment. The time horizon was one year. SMC clinical experts have indicated that atomoxetine is the comparator most likely to be displaced in Scotland. However, it should be noted that clonidine has also been identified as a possible comparator. This treatment is currently used off-label but has not been included as a relevant comparator within the economic analysis.

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, as noted above, 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 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.

Medicine costs were included in the analysis and were based on a weighted average approach whereby patient distribution data for guanfacine were taken from study SPD503-316. The analysis included the per cycle cost of both the titration phase and the post-titration period. Monitoring costs were assumed to apply to both responders and non-responders and included costs associated with psychiatrist, paediatrician, GP and nurse visits as well as ECG and blood tests. It was assumed that responders required fewer clinician visits compared to non-responders.

Utility values were taken from a conference abstract which described a UK study where EQ-5D data were collected from parents/caregivers. Responders and non-responders had utility values of 0.837 and 0.773 respectively.

The submitting company estimated an incremental cost-effectiveness ratio (ICER) of £13,455 per quality-adjusted life-year (QALY) compared to atomoxetine, based on an incremental cost of £82 and an incremental QALY gain of 0.006. The incremental costs stem from increased medicine costs while the incremental QALY gain stems from the increased response rate and therefore improved quality of life associated with guanfacine treatment.

The company provided one-way and scenario-based sensitivity analyses. Results were most sensitive to the use of efficacy data from the NMA. 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. Results were also sensitive to a 20% decrease in non-responder medical costs, resulting in an ICER £22,891. In addition, the impact of increasing atomoxetine efficacy was also considered in order to capture the possibility of a change in efficacy after the study. When the response rate was increased from 70% to 72%, the ICER increased to £19,847.

The primary weakness within the analysis relates to the following;

- As noted above, there are issues regarding the comparative data between guanfacine and atomoxetine in terms of not being controlled for multiplicity and also in the statistical power of the study. This meant there were some concerns about the robustness of the clinical data that have been used to drive the economic model. As such, the submitting company was asked to provide a conservative analysis assuming that the treatments were equivalent i.e. a cost-minimisation analysis (CMA). The results of the CMA 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.
- In the base case analysis, all patients responding to treatment (at the end of the titration period) are assumed to remain in the response health state for the duration of the model. Due to the uncertainty surrounding this assumption, the company was asked to provide 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). 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.

Despite the limitations outlined above, the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- A joint submission was received from four Scottish ADHD Parent Groups: ADHD Parent Support West Glasgow, Mindroom, Dundee and Angus ADHD Support Group and Perth & Kinross ADHD Support Group. All are registered charities apart from ADHD Support West Glasgow which is a charitable unincorporated organisation.
- None of the four groups have received any funding from pharmaceutical companies in the past two years.
- ADHD has a profound effect on children with it and on their wider families. It has effects on the children not just in childhood but in terms of reduced life chances resulting from poor performance at school, school exclusion, poor self esteem, risk taking behaviour and difficulties in sustaining relationships. It also has a huge impact on the parents, siblings and wider family of the child, leading in many cases to marital conflict, stress, anxiety and even family breakdown.
- Parents are naturally reluctant to medicate their children. However, 65% of respondents to a survey conducted by the patient groups agreed or strongly agreed that the benefits of medication outweighed the drawbacks for their child. Nonetheless, problems with side effects mean that, for some children, currently available ADHD medications are not suitable. Hence the availability of more medication options for discussion with parents by treating psychiatrists would be very beneficial.
- 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.

Additional information: guidelines and protocols

The British Association for Psychopharmacology (BAP) published the guideline 'Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology' in 2014. The guideline recommends that all children with severe ADHD (conceptualised as hyperkinetic disorder) should be offered pharmacological treatment; a psychostimulant medication is recommended first-line. Atomoxetine is an alternative when there is a risk of misuse of psychostimulants (by children or by the adults supporting the child). In addition, pharmacological treatment should be considered for children with moderate symptoms of ADHD who have not responded to psychological interventions.¹⁴

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 March 2013). 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.¹⁵

The Scottish Intercollegiate Guidelines Network (SIGN) produced clinical guideline SIGN112, 'Management of attention deficit and hyperkinetic disorders in children and young people' in October 2009. At the time of publication, three medicines were licensed for use in the treatment of ADHD: methylphenidate and atomoxetine in children aged six years or older; and dexamfetamine in children aged three years or older. The guideline recommends the psychostimulants methylphenidate and dexamfetamine as first-line medication in school-age children with moderate/severe ADHD (unless there are known cardiac abnormalities). Atomoxetine, which is a non-psychostimulant, is recommended as treatment for the core symptoms of ADHD in children where psychostimulant medication is not appropriate, not tolerated or is ineffective.¹³

All of these treatment guidelines predate the availability of guanfacine for the treatment of ADHD.

Additional information: comparators

Atomoxetine, clonidine*.

*Not licensed in the UK for the treatment of ADHD

Cost of relevant comparators

| Drug | Dose Regimen | Cost per year (£) |
|------------------------|--|-------------------|
| Guanfacine | 1 to 7mg orally once daily, dependent on age and weight (consult SPC). | 728 to 1842 |
| Atomoxetine | 10 to 100mg orally in one or two divided doses, dependent on age and weight (consult SPC). | 812 to 1083 |
| Clonidine [†] | 50 to 300micrograms orally once daily, dependent on age and weight. | 45 to 88 |

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS Online 30/10/15 (except guanfacine cost which is from the company submission). SPC=summary of product characteristics. [†]Clonidine is not licensed in the UK for the treatment of ADHD; dose based on advice from clinical experts consulted by SMC.

Additional information: 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.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

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This assessment is based on data submitted by the applicant company up to and including 11 December 2015

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.