

▼ **Guanfacine (Intuniv®) for Attention Deficit Hyperactivity Disorder (ADHD) in school aged children, adolescents and adults**

Introduction	
General Statements	<ul style="list-style-type: none"> • This guideline sets out details for the shared care of patients taking guanfacine. • This guideline follows the recommendations of NICE clinical guideline No 72 (NICE CG72), NICE Technology Appraisal No 98 (Review of No 13) and SIGN Guideline 112. • Agreement of the GP should be sought before seeking patient agreement for shared care. • Prior to seeking shared care with the patient's GP <ol style="list-style-type: none"> 1. The patient's clinical condition will be stable or predictable. 2. The patient will have been stabilised on the drug with time allowed for common adverse events and side-effects to have occurred. • The GP must reply in writing to the request for shared care within two weeks if unwilling to participate. • The full summary of product characteristics for guanfacine should be read before prescribing. www.medicines.org.uk • Guanfacine is unlicensed for the use in adults with ADHD. • This guideline relates to children, adolescents and adults with moderate to severe ADHD • Patients will receive prescriptions for supplies of medication from secondary care until shared care is agreed with the primary care doctor. • If a patient changes GP then the new GP and the Secondary Care Prescriber should discuss setting up shared care for the patient.
Background	<p>NICE clinical guideline No 72 states</p> <p>Diagnosis of ADHD</p> <ul style="list-style-type: none"> • Diagnosis should only be made by a specialist psychiatrist, paediatrician or other healthcare professional with training and expertise in the diagnosis of ADHD. • Diagnosis should be based on: <ul style="list-style-type: none"> – a full clinical and psychosocial assessment. Discuss behaviour and symptoms in the different domains and settings of the person's everyday life – a full developmental and psychiatric history, and – observer reports and an assessment of mental state. • Diagnosis should be made when symptoms of hyperactivity/impulsivity and/or inattention: <ul style="list-style-type: none"> – meet the criteria in DSM-IV or ICD-10 (hyperkinetic disorder),

	<p style="text-align: center;">and</p> <ul style="list-style-type: none"> – are associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or observation in multiple settings, and – are pervasive, occurring in at least two settings. <ul style="list-style-type: none"> • As part of the diagnostic process, include an assessment of needs, coexisting conditions, social, familial and educational or occupational circumstances and physical health. For children and young people also include an assessment of the parents’ or carer’s mental health. <p>Drug treatment in children and young people</p> <ul style="list-style-type: none"> • Drug treatment should: <ul style="list-style-type: none"> – only be started by a healthcare professional with expertise in ADHD – be based on comprehensive assessment – always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. • Drug treatment is not indicated as the first-line treatment for all school-age children and young people with ADHD. It should be reserved for those with severe symptoms and impairment or for those with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group psychological treatment. • Consider guanfacine in children of 6 years and older when symptoms are unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine. • Consider Intuniv® (guanfacine) in children aged 6 years and over when response to previous methylphenidate treatment is considered clinically inadequate. <p>Drug treatment in adults</p> <ul style="list-style-type: none"> • NICE CG72 recommends pharmacological intervention as the first line treatment for adults with ADHD symptoms causing moderate to severe impairment. • Guanfacine may be considered in adults unresponsive to or intolerant to an adequate trial of methylphenidate or atomoxetine or where the treatment is considered clinically inadequate or contra-indicated. • In adults whose symptoms persist into adulthood and who have shown clear benefit from guanfacine treatment, it may be appropriate to continue treatment into adulthood. • GPs may continue prescribing and monitoring drug treatment under shared care arrangements. • If improvement of symptoms is not seen after appropriate dose adjustment, guanfacine will be discontinued.
Pharmacology	Guanfacine is a selective alpha _{2A} -adrenergic receptor agonist in that it

	has 15-20 times higher affinity for this receptor subtype than for the alpha _{2B} or alpha _{2C} subtypes. Guanfacine is a non-stimulant. The mode of action of guanfacine in ADHD is not fully established. Preclinical research suggests guanfacine modulates signalling in the prefrontal cortex and basal ganglia through direct modification of synaptic noradrenalin transmission at the alpha 2- adrenergic receptors.
Indication	<ul style="list-style-type: none"> Guanfacine is indicated (as part of a comprehensive treatment programme), for the treatment of ADHD in children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Guanfacine is unlicensed for the use in adults with ADHD but may be used in accordance with NICE guidance as described above.

Individuals Responsibilities	
Hospital Specialist's Responsibilities	<ol style="list-style-type: none"> Confirm the diagnosis of ADHD following full assessment, drawing upon information from all sources and first hand observation of the service user. If prescribing for adults discuss the unlicensed status of the treatment and the implications and obtain consent. Before starting drug treatment children, young people and adults with ADHD should have a full pre-treatment assessment, which should include: <ul style="list-style-type: none"> a full mental health and social assessment a full history and physical examination, including: <ul style="list-style-type: none"> risk of somnolence and sedation, hypotension and bradycardia, QT-prolongation arrhythmia and weight increase /risk of obesity. cardiovascular status including blood pressure and heart rate (plotted on chart), comprehensive history of concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death accurate recording of pre-treatment height and weight on a growth chart Initiation of guanfacine therapy and monitoring during dose titration and on-going monitoring until shared care is agreed. <p><i>Monitoring during titration</i> Weekly monitoring for signs and symptoms of somnolence and sedation, hypotension and bradycardia should be performed.</p> <p><i>Ongoing monitoring until shared care agreed.</i> During the first year of treatment, the patient should be assessed at least every 3 months for signs and symptoms of:</p> <ul style="list-style-type: none"> somnolence and sedation hypotension bradycardia weight increase /risk of obesity. <p>6 monthly monitoring should follow thereafter, with more frequent monitoring following any dose adjustments.</p> <ol style="list-style-type: none"> Supply of the medicines for one further month after the dose has

	<p>been stabilised and efficacy established.</p> <ol style="list-style-type: none"> 2. Prescribe guanfacine until GP formally agrees to share care. 3. Review continued safety and efficacy at least once a year 4. Monitor height and weight at these appointments. 5. Review the need for treatment at school leaving age and if necessary arrange transition to adult services. 6. Arrange shared care with the GP once stabilised on medication 7. Adjusting treatment as appropriate e.g. varying dosage or timing, periods without treatment, and informing the GP of any changes in writing. 8. Inform and decide with GP any action if patient misses an appointment. 9. Stopping treatment when appropriate. <p>Patient Information to be received by the GP from the Consultant</p> <ul style="list-style-type: none"> • The specialist’s review letter - sent after initial assessment and following each further appointment should include any changes to the patient’s medication regimen. • When dose titration has been completed and the treatment is stable the GP could be asked by the specialist to continue prescribing and monitoring under a shared care arrangement and sent a copy of this Shared Care Guideline.
<p>General Practitioner’s Responsibilities</p>	<ol style="list-style-type: none"> 1. Initial referral to a Consultant Child and Adolescent Psychiatrist, Consultant Paediatrician with expertise in ADHD or specialist Adult ADHD services, raising the possibility of ADHD. 2. The GP must reply in writing to the request for shared care within two weeks if unwilling to participate in shared care. 3. Arrange to see the patient on a regular basis to monitor their health and well-being (at least three monthly). This includes undertaking any necessary physical health monitoring to ensure that monitoring requirements are maintained beyond Specialist review appointments (see below). 4. Report and discuss with Specialist any adverse effects of medication, possible drug interactions or deteriorating behaviour. 5. Upon acceptance of shared care, provide the patient with prescriptions of guanfacine. 6. To only continue prescriptions if monitoring compliance and results are satisfactory. It would be good practice to only issue acutely i.e. not to have on a repeatable prescription. 7. To ensure no drug interactions with concomitant medicines. <p><i>Ongoing monitoring once shared care agreed</i></p> <p>During the first year of treatment, the patient should be assessed at least every 3 months for signs and symptoms of:</p> <ul style="list-style-type: none"> ○ somnolence and sedation ○ hypotension ○ bradycardia ○ weight increase /risk of obesity

	<p>6 monthly monitoring should follow thereafter. (More frequent monitoring following any dose adjustments to be carried out by Secondary care).</p> <p>Patient Information to be received by the Consultant from the GP</p> <ul style="list-style-type: none"> • Details of any adverse effects experienced by the patient. • Any relevant medical information including any test results. • Any changes to the patient's medication regimen.
Joint Responsibilities	<p>It is the joint responsibility of the GP and Consultant to ensure the patient/parent/ carer are aware of their responsibilities:</p> <ol style="list-style-type: none"> 1. To attend appointments 2. To have the recommended tests 3. To inform the GP if health problems arise 4. To be aware of side effects listed in the patient information leaflet supplied with the medication and report any relevant symptoms.
When and How to Discontinue Treatment	<ul style="list-style-type: none"> • Patients/caregivers should be instructed not to discontinue guanfacine without consulting a healthcare professional, preferably their Consultant or ADHD clinic. • Tapering guanfacine dosing during withdrawal is recommended to minimise potential withdrawal effects including rebound hypertension and sedation • Decrements of no more than 1mg every 3 to 7 days should be undertaken. • Blood pressure and pulse may increase during and following discontinuation of guanfacine.
Information given to the patient	<p>A pharmaceutical company patient information leaflet (PIL) will be provided with each supply.</p> <p>Patients should be advised that somnolence and sedation can occur, particularly early in treatment or with dose increases. If somnolence and sedation are judged to be clinically concerning or persistent, a dose decrease or discontinuation should be considered.</p> <p>Information is available in different formats and languages on www.choiceandmedication.org/swyp</p> <p>NICE's website address for further information is www.nice.org.uk.</p>
Contact Details	To be included in specialist's letter

Product Information	
The information in this Shared Care Guideline should be used in conjunction with the latest edition of the BNF and Summary of Product Characteristics	
Dosage and Administration	<ul style="list-style-type: none"> • 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, age and weight. • The recommended maintenance dose range is 0.05-0.12 mg/kg/day.

	<ul style="list-style-type: none"> • If using guanfacine for extended periods (over 12 months), usefulness of guanfacine should be assessed every 3 months for the first year and then at least yearly. • Consider trial periods off medication to assess the patient's functioning without pharmacotherapy, preferably during times of school holidays.
<p>Adverse Effects</p> <p>▼ This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.</p>	<p>Significant side-effects</p> <p>Very common Somnolence (which may last 2-3 weeks), headache, abdominal pain and fatigue</p> <p>Common Decreased appetite, anxiety, depression and labile mood, sleep disturbances, sedation, bradycardia and hypotension, gastro-intestinal disturbances, weight increase, rash</p> <p>Uncommon but significant Asthma, arrhythmias and AV block, chest pain</p> <p>Rare Hypertension, malaise, hypersomnia</p>
<p>Precautions and Contra-indications</p>	<ul style="list-style-type: none"> • Cautions Hypotension, bradycardia and syncope which could result in falls or accidents. Caution is advised when treating patients with guanfacine who have a history of hypotension, heart block, bradycardia, or cardiovascular disease, or who have a history of syncope or a condition that may predispose them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Caution is also advised when treating patients with guanfacine who are being treated concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Patients should be advised to drink plenty of fluid. <p>QTc interval Guanfacine should be prescribed with caution in patients with a known history of QT prolongation, risk factors for torsade de pointes (e.g. heart block, bradycardia, hypokalemia) or patients who are taking medicinal products known to prolong the QT interval. These patients should receive further cardiac evaluation based on clinical judgement.</p> <ul style="list-style-type: none"> • Driving May affect performance of skilled tasks (e.g. driving); Patients should not drink alcohol. <p>Suicidal ideation Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible change in the ADHD treatment programme.</p> <p>Contra-indications Hypersensitivity to any ingredients</p>

	<ul style="list-style-type: none"> • Renal impairment Dosage reduction may be required in severe renal impairment and end stage renal disease. • Pregnancy Guanfacine is not recommended during pregnancy and in women of child bearing potential not using contraception. • Breast-feeding It is not known if guanfacine is excreted in breast milk. 																														
<p>Clinically relevant Drug Interactions and their management</p>	<ul style="list-style-type: none"> • The pharmacodynamic effect of guanfacine can have an additive effect when taken with other products known to cause <ul style="list-style-type: none"> ○ sedation (eg CNS depressants such as hypnotics, antidepressants or alcohol) ○ hypotension (eg antihypertensives) or ○ QT prolongation (eg antipsychotics) • CYP3A4/5 inhibitors and inducers, plasma concentrations of guanfacine may be elevated or lowered, potentially affecting the efficacy and safety of guanfacine. Guanfacine can increase plasma concentrations of concomitantly administered medicinal products that are metabolised via CYP3A4/5. <p><u>CYP3A4 and CYP3A5 inhibitors</u></p> <ul style="list-style-type: none"> • Caution in patients taking ketoconazole and other moderate and strong CYP3A4/5 inhibitors; a decrease in the dose of guanfacine within the recommended dose range is recommended. • Moderate and strong CYP3A4/5 inhibitors elevate plasma guanfacine; concentrations and increases the risk of adverse reactions such as hypotension, bradycardia, and sedation. <p><u>CYP3A4 inducers</u></p> <p>Concomitantly administration of guanfacine with a CYP3A4 inducer, an increase in the dose of guanfacine within the recommended dose range is recommended.</p> <p><i>This list is not definitive</i></p> <table border="1" data-bbox="496 1485 1398 1951"> <thead> <tr> <th>Moderate CYP3A4/5 inhibitors</th> <th>Strong CYP3A4/5 inhibitors</th> <th>CYP3A4 inducers</th> </tr> </thead> <tbody> <tr> <td>Aprepitant</td> <td>Boceprevir</td> <td>Bosentan</td> </tr> <tr> <td>Atazanavir</td> <td>Chloramphenicol</td> <td>Carbamazepine</td> </tr> <tr> <td>Ciprofloxacin</td> <td>Clarithromycin</td> <td>Efavirenz</td> </tr> <tr> <td>Crizotinib</td> <td>Indinavir</td> <td>Etravirine</td> </tr> <tr> <td>Diltiazem</td> <td>Itraconazole</td> <td>Modafinil</td> </tr> <tr> <td>Erythromycin</td> <td>Ketoconazole</td> <td>Nevirapine</td> </tr> <tr> <td>Fluconazole</td> <td>Posaconazole</td> <td>Oxcarbazepine</td> </tr> <tr> <td>Fosamprenavir</td> <td>Ritonavir</td> <td>Phenobarbital</td> </tr> <tr> <td>Imatinib</td> <td>Saquinavir</td> <td>Phenytoin</td> </tr> </tbody> </table>	Moderate CYP3A4/5 inhibitors	Strong CYP3A4/5 inhibitors	CYP3A4 inducers	Aprepitant	Boceprevir	Bosentan	Atazanavir	Chloramphenicol	Carbamazepine	Ciprofloxacin	Clarithromycin	Efavirenz	Crizotinib	Indinavir	Etravirine	Diltiazem	Itraconazole	Modafinil	Erythromycin	Ketoconazole	Nevirapine	Fluconazole	Posaconazole	Oxcarbazepine	Fosamprenavir	Ritonavir	Phenobarbital	Imatinib	Saquinavir	Phenytoin
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Imatinib	Saquinavir	Phenytoin																													

	Verapamil	Suboxone	Primidone
	Grapefruit juice	Telaprevir	Rifabutin
		Telithromycin	Rifampicin
			St. John's Wort

- **Valproic acid.** Concentrations of valproic acid may be increased with concomitant administration of guanfacine, monitoring for adverse effects is recommended and dose adjustment may be required.
- **High fat meals** significantly increase absorption of guanfacine.

References	
References	<ul style="list-style-type: none"> • SPC for Intuniv®. • NICE Technology Appraisal No 98. – Methylphenidate, atomoxetine and guanfacine for attention deficit hyperactivity disorder (ADHD) in children and adolescents. • NICE clinical guideline No 72. – Attention deficit hyperactivity disorder - Diagnosis and management of ADHD in children, young people and adults.

Appendix 1

Table 1

Dose Titration Schedule for Children Aged 6-12 years				
Weight Group	Week 1	Week 2	Week 3	Week 4
25 kg and up Max Dose= 4 mg	1 mg	2 mg	3 mg	4 mg

Table 2

Dose Titration Schedule for Adolescents (aged 13-17 years) and Adults							
Weight Group ^a	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
34-41.4 kg Max Dose= 4 mg	1 mg	2 mg	3 mg	4 mg			
41.5-49.4 kg Max Dose= 5 mg	1 mg	2 mg	3 mg	4 mg	5 mg		
49.5-58.4 kg Max Dose= 6 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	
58.5 kg and above Max Dose= 7 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg ^b

^a Adolescent subjects must weigh at least 34kg.

^b Adolescents weighing 58.5 and above may be titrated to a 7mg/day dose after the subject has completed a minimum of 1 week of therapy on a 6mg/day dose and the physician has performed a thorough review of the subject's tolerability and efficacy.