Central and North West London NHS Foundation Trust - New Medicines Review

Guanfacine hydrochloride (Intuniv®) 1mg, 2mg, 3mg and 4mg prolonged release tablets in children and young people
(Launched by Shire Pharmaceuticals Ltd in January 2016)
Date of review March 2016

This was approved for addition to the formulary at the April 2016 Medicines Management Group as per following:
- In accordance with the license in ages 6 to 17 years for whom stimulants are not suitable
- It can only be initiated by a consultant
- It can only be prescribed if able to carry out all the monitoring in accordance with the license/ Summary of Product Characteristics
- It can only be prescribe if it is possible to continue prescribing within secondary care

Background and licensed indication

Guanfacine extended release (Intuniv®) is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescent, 6 to 17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Intuniv® must be used as part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures. Treatment must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders. It is not licensed for use in combination with stimulants or for adults with ADHD.

Guanfacine is a non-stimulant and a selective α2A– adrenoreceptor agonist that acts preferentially on post-synaptic α2A – adrenoreceptors. The mode of action of guanfacine in ADHD is not fully established. It is suggested that α2A stimulation increases delay-related firing of prefrontal cortex neurons, and improves the symptoms associated with ADHD. Preclinical research suggests guanfacine modulates signalling in the prefrontal cortex and basal ganglia through direct modification of synaptic noradrenaline transmission at the alpha 2- adrenergic receptors.

The NICE Clinical guideline (CG72) for diagnosis and management of ADHD in children, young people and adults advises where pharmacological treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended.

Dosing

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 1mg per week.

Intuniv® should not be crushed, chewed or broken before swallowing because this increases the rate of guanfacine release.

The recommended maintenance dose range is 0.05 – 0.12mg/kg/day, based on the patient’s response and tolerability. Dose adjustments (increase or decrease) to a maximum tolerated dose within the recommended optimal weight-adjusted dose range may occur at any weekly interval after the initial dose. The recommended dose titration for children and adolescents is detailed in table 1 & 2 below.

Table 1

<table>
<thead>
<tr>
<th>Dose Titration Schedule for Children (6 – 12 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Group</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>25kg and up</td>
</tr>
<tr>
<td>Max Dose = 4mg</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Dose Titration Schedule for Adolescents (13 – 17 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Group</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>34-41.4kg</td>
</tr>
<tr>
<td>Max Dose =</td>
</tr>
</tbody>
</table>
Guanfacine can cause syncope, hypotension, bradycardia, somnolence, sedation weight gain and QT interval prolongation.

Careful dose titration and monitoring is necessary at the start of treatment with Intuniv® since clinical improvement and risks for several clinical significant adverse reactions (syncope, hypotension, bradycardia, somnolence and sedation) are dose and exposure related.1,4

**Monitoring:**
**Pre-treatment:** Prior to prescribing, it is necessary to conduct a baseline evaluation to identify patients at increased risk of somnolence and sedation, hypotension and bradycardia, QT-prolongation arrhythmia and weight increase /risk of obesity. This evaluation should address a patient’s cardiovascular status including blood pressure and heart rate, documenting comprehensive history of concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart.

During dose titration, weekly monitoring for signs and symptoms of somnolence and sedation, hypotension and bradycardia should be performed.1

**Ongoing monitoring:**
During the first year of treatment, the patient should be assessed at least every 3 months.1

<table>
<thead>
<tr>
<th>Monitor the signs and symptoms</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence and sedation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hypotension</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Weight increase/risk of obesity</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

- After the first year, 6 monthly monitoring should follow thereafter.1
- More frequent monitoring following any dose adjustments.1
- Consider trial periods off medication to assess the patient’s functioning without pharmacotherapy, preferably during times of school holidays.1

**Downward titration and discontinuation:**1
Blood pressure and pulse may increase following discontinuation of guanfacine, and should be monitored in all patients during dose downward titration. (Dose reduction of no more than 1mg every 3 to 7 days). Taper Intuniv® dosing during withdrawal is recommended to minimise these potential withdrawal effects. Patients/caregivers should be instructed not to discontinue guanfacine without consulting their physician.

**Missed Dose:**1
In the event of missed dose, Intuniv® dosing can resume the next day. If two or more consecutive doses are missed, re-titration is recommended based on the patient’s tolerability to guanfacine.

**Special populations:**1
Guanfacine is not licensed in adults or elderly population, the safety and efficacy in adult and the elderly with ADHD has not been established.

**Hepatic impairment**

Guanfacine is cleared both by the liver and the kidneys, and at least 50% of the clearance of guanfacine is hepatic. Dose reduction may be required in patients with different degrees of hepatic impairment. The impact of hepatic impairment on the pharmacokinetics of guanfacine in children and adolescents (6-17 years old) is unknown.

**Renal impairment**

Guanfacine is cleared both by the liver and the kidneys, with approximately 30% of an intact medicinal product excreted with urine. Dose reduction may be required in patients with severe renal impairment (GFR 29-15 ml/min) and an end stage renal disease (GFR<15 ml/min) or requiring dialysis. The impact of renal impairment on the pharmacokinetics of guanfacine in children and adolescents (6-17 years old) is unknown.

**Children under 6 years**

Intuniv® should not be used in children under the age of 6 years because efficacy and safety in this patient population has not been studied.

**Patients treated with CYP3A4 and CYP3A5 inhibitors /inducers**

CYP3A4/5 inhibitors have been shown to have a significant effect on the pharmacokinetics of guanfacine when co-administered. Dose adjustment is recommended with concomitant use of moderate/strong CYP3A4/5 inhibitors (e.g. ketoconazole, grapefruit juice), or strong CYP3A4 inducers (e.g. carbamazepine).

**Alternatives**

Atomoxetine (Strattera®) is the only other non-stimulants licensed for ADHD treatment available in UK (as capsules and oral solution). Other treatment options include bupropion, clonidine, modafinil and imipramine, which are unlicensed or off-label medicines for ADHD should be initiated following a referral to tertiary services.

**NICE**

Guanfacine (Intuniv®) is accepted for use within NHS Scotland (SMC, 8 Jan 2016)³ for the treatment of ADHD in child and adolescents (6-17 years old) for whom stimulants are not suitable, or 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. The approval was largely based on two pivotal Phase III studies ⁵,⁶ (Hervas et al & Newcorn et al) in children and adolescents aged 6 to 17 years with ADHD which demonstrated that guanfacine improved the symptoms of ADHD compared to placebo.

The NICE guideline on ADHD recommends that pharmacological treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice an interventions. Where pharmacological treatment is appropriate, the guideline recommends methylphenidate, atomoxetine and dexamfetamine, within their licensed indication, as options.² NICE guidelines recommends methylphenidate or atomoxetine first, with dexamfetamine a consideration in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine.² If unresponsive to methylphenidate, atomoxetine and dexamfetamine, further treatment (such as bupropion, clonidine, modafinil and Imipramine, which are unlicensed or off-label medication for ADHD) should only follow after referral to tertiary services.²

A recent NICE Evidence Summary for Guanfacine (Intuniv®)² published on 22 March 2016 noted guanfacine was more effective than placebo at improving ADHD symptoms in 3 short-term randomised controlled trials⁵,⁶,⁷ (Hervas, Newcorn, Wilens), although a beneficial effect on social functioning was not consistently shown.

**Clinical studies**

Guanfacine/Intuniv® is approved in USA by FDA since 2009 for the management of ADHD in children and adolescents. The FDA approval was based on two studies ⁸,⁹ (Biederman et al 2008,
Sallee et al, 2009b) at the time.

**Efficacy** is demonstrated by short term RCT studies only with placebo control. There are no studies that directly compare the efficacy and safety of guanfacine prolonged release with other active treatments for ADHD.

A randomised, controlled phase III study\(^5\) by *Hervas et al* evaluated the efficacy and safety of extended-release guanfacine hydrochloride (GXR) in children and adolescents (6-17 years) with ADHD (n=338). Patients received GXR (between 1-7mg/day depending on age and weight), atomoxetine (ATX; 10-100mg/day) or placebo for 4 or 7 weeks. The primary efficacy measure was change from baseline in ADHD Rating Scale version IV (ADHD-RS-IV). Of the 338 patients randomised, 272 (80.5%) completed the study. The placebo-adjusted difference in least square (LS) mean change from baseline in ADHD-RS-IV total score for GXR was −8.9 (95% CI, −11.9, −5.8, \(p<0.001\)), and for ATX was −3.8 (−6.8, −0.7, \(p=0.017\); 0.32) and found to be statistically significant. In this study, the onset of treatment action observed was more rapid with GXR than ATX. GXR achieved a statistical separation from placebo at Week 1 (\(p=0.001\)) versus Week 3 for ATX (\(p=0.024\)), as measured by the ADHD-RS-IV score.\(^5\)

Although the study contained an Atomoxetine arm, the study design was limited by a lack of direct comparison between guanfacine to an active comparator.

Eighty-eight (77.2%) patients in the GXR, 76 (67.9%) in the ATX and 73(65.8%) in the placebo groups experienced Treatment Emergent Adverse Effects (TEAEs) during the study. Somnolence (43.9% vs. 17.9%), headache (26.3% vs.19.6%) and fatigue (25.4% vs.21.4%) were more frequently reported in patients treated with GXR than in those who received ATX respectively. The most common adverse effects reported were consistent with the known safety profiles of GXR from previous trials.\(^5\)

A phase III, double-blinded, placebo controlled randomised-withdrawal study\(^6\) by *Newcorn et al* evaluated the long-term maintenance of guanfacine efficacy in children and adolescents with ADHD. Patients received open-label GXR (1-7mg/day), after 13 weeks, responders were randomised to GXR or placebo in the 26 week, double-blind, randomised-withdrawal phase (RWP). The primary endpoint was the percentage of treatment failure measured by >50% increase in ADHD-RS-IV and ≥2 point increase in Clinical Global Impression-Severity (CGSI) score compared with RWP baseline. The key secondary endpoint was time to treatment failure (TTF). A total of 528 participants enrolled, 316 entered the RWP. There was a high dropout rate in both groups. A significantly smaller proportion of patients treated with GXR (49%; 95% CI; 41 to 57) were classed as treatment failures during this phase compared with placebo (65%; 95% CI: 57 to 72); Treatment difference -16% (95% CI: -27 to -4.5). Patient in the GXR group had a significantly longer time to treatment failure (median 218 days; 95% CI) compared with the placebo group (median 56 days; 95% CI: 44 to 97); \(p=0.003\).\(^6\)

A randomised, placebo-controlled trial\(^7\) by *Wilens et al* evaluated the safety and efficacy of GXR in Adolescents with ADHD. This 13 week, multicenter evaluated once-daily GXR (1-7mg per day) in adolescents with ADHD aged 13-17 years. The primary endpoint was the change from baseline in the ADHD-RS-IV total score; key secondary endpoints included CGSI-scores and Learning and School domain and Family domain scores at Week 13. A total of 314 participants were randomised (GXR, n=157; placebo, n=157) to receive optimal doses of 3,4,5 or 6mg with 46.5% receiving more than 4mg/day. GXR group showed improvement in ADHD-RS-IV score compared to placebo (least square mean score change, −24.55[GXR] versus -18.53[placebo]; effect 0.52, \(p<0.001\)). There was also a significant improvement (\(p=0.01\)) in CGI-S scores for guanfacine compared with placebo (50.6% versus 36.1 %), respectively.\(^7\)

The *Sallee et al* study\(^8\) compared the efficacy of GXR with placebo in children and adolescent with ADHD in a double-blind multi-centre trial. Patients (n=324) were randomised with GXR 1mg, 2mg 3mg and 4mg doses or placebo over 9 weeks. Statistically significant reductions in ADHD-RS-IV scores were observed from baseline to endpoint at all dose of GXR was -19.6 (SD13.9) compared with -12.2 (SD 13.0) for placebo, with effect sizes ranging from 0.43 to 0.62. In subjects receiving GXR, mean heart rate and systolic/diastolic blood pressure decreased as the dose of GXR
increased, and then returned toward baseline during the dose-maintenance and dose-tapering phases of the trial.

A randomised double blind, placebo–controlled study by **Biederman et al** assessed the efficacy and safety of GXR in children and adolescent with ADHD. The patients (n=345) aged 6-17 years were randomly and assigned to 1 of 3 treatment groups (2,3 or 4mg.day) or placebo for 6 weeks. Least-squares mean changes from baseline to the end point in ADHD-RS-IV score was significant in all groups taking GXR: 2mg,3mg and 4mg groups were -7.70(95% CI:-12.25 to -3.15; P=0.002), -7.95 (95% CI:-12.50 to -.340; P=0.001), and -10.39 (95% CI: -14.97 to -5.82; P<0.0001) respectively.

The authors found the most commonly reported TEAEs were somnolence, fatigue, upper abdominal pain and sedation. Most of the commonly reported TEAEs were mild or moderate in intensity. The median day of onset of fatigue was within the first week of dosing, whereas the median days of onset for somnolence and sedation were with the first 2 weeks of dosing.

A long term, open-label extension study was conducted by same authors **Biederman et al** to assess the safety profile of guanfacine for up to 2 years. GXR was initiated at 2mg/day and titrated as needed in 1mg increments to a maximum of 4mg/day. The secondary objective was assessment of long-term effectiveness using ADHD-RS-IV. 240 out of 345 patients were enrolled from previous trial. A total of 198 patients did not complete the study; the most common reason for discontinuation was withdrawal of consent (34%). About 26% of the study withdrawals were related to adverse effects. Somnolence, headache, fatigue and sedation were the most frequently reported TEAEs. The highest rates of study discontinuation were due to somnolence (3.8%), weight increase (2.9%) and fatigue (2.1%). These adverse effects were usually mild or moderate in severity and appeared to be dose related. The prevalence rate was highest during the first month of the study and generally diminished over subsequent months. For primary effectiveness outcome, the mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (-18.1, P<.001). However, the study limitations were open label trial, the maximum GXR dosage prescribed over the course of 2 years was 4mg/day, the sample was not powered, and there was a large dropout rate.

### Safety

As noted by both SMC (Scottish Medicines Consortium) and NICE ESNM70 summary reports, there are no long term controlled studies to demonstrate clinical efficacy or safety of guanfacine in children and adolescents with ADHD. Hence, the long term efficacy and safety of guanfacine is unknown. Two open label extension studies reported on long-term effectiveness of guanfacine for up to 2 years. Although there were clinically meaningful reductions on the ADHD-RS-IV scores, the discontinuation rates were high with approximately 80% of participants across the 2 studies leaving before 24 months.

There is also a lack of direct head to head clinical studies with alternative stimulant medication available in children and adolescents with ADHD.

From clinical studies, the most frequently reported adverse reactions (very common) include somnolence (40.6%), headache (27.4%), fatigue (18.1%), abdominal pain upper (12.0%), and sedation (10.2%). The adverse reactions somnolence and sedation occurred predominately at the start of treatment and may typically last for 2-3 weeks and longer in some cases. Before Intuniv® is used with any other centrally active depressants (such as alcohol, sedatives, phenothiazines, barbiturates, or benzodiazepines) the potential for additive sedative effects should be considered.

**Serious adverse reactions commonly reported** include hypotension (3.2%), weight increase (2.9%), bradycardia (1.5%) and syncope (uncommon 0.7%).

After discontinuation, in particular after abrupt cessation of treatment, rebound hypertension and tachycardia may occur.

The EPAR concluded that the safety of guanfacine was considered to be acceptable. However, the manufacturer is required to conduct a post-authorisation study in order to investigate the long-term safety (especially effects on neurocognitive function) of guanfacine.
Refer to Summary of Product Characteristics (SPC) for complete list of adverse reactions.

Caution is also advised when treating patients with Intuniv® 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.

### CYP3A4 and CYP3A5 inhibitors

Caution should be used when Intuniv® is administered to patients taking ketoconazole and other moderate and strong CYP3A4/5 inhibitors; a decrease in the dose of Intuniv within the recommended dose range is proposed. Co-administration of Intuniv with moderate and strong CYP3A4/5 inhibitors elevates plasma guanfacine concentrations and increases the risk of adverse reactions such as hypotension, bradycardia, and sedation. In case of concomitant use of strong and moderate CYP3A inhibitors, a 50% reduction of the guanfacine dose is recommended. Due to variability in interaction effect, further dose titration may be needed.

### CYP3A4 inducers

When patients are taking Intuniv concomitantly with a CYP3A4 inducer, an increase in the dose of Intuniv within the recommended dose range is proposed. There was a significant decrease in the rate and extent of guanfacine exposure when co-administered with rifampicin, a CYP3A4 inducer. If guanfacine is combined with strong enzyme inducers, a retitration to increase the dose up to a maximum daily dose 7mg may be considered if needed. If the inducing treatment is ended, retitration to reduce the guanfacine dose is recommended during the following weeks.

### Food interactions

Intuniv should not be administered with high fat meals due to increased exposure, as it has been shown that high fat meals have a significant effect on the absorption of guanfacine.

Patients should not drink alcohol whilst taking Intuniv®. Patients are advised against operating heavy equipment, driving or cycling until they know how they respond to treatment with Intuniv.

### Convenience

Prolonged-release oral formulation, with once daily administration either in morning or evening time.

Intuniv® should not be crushed, chewed or broken before swallowing because this increases the rate of guanfacine release.

Treatment is recommended only for children who are able to swallow the tablet whole without problems.

Intuniv® can be administered with or without food but should not be administered with high fat meals, due to increased exposure.

Intuniv® should not be administered together with grapefruit juice.

Guanfacine is a non-stimulant, therefore it is less risk of diversion or misuse compared to stimulant medications usually prescribed for ADHD.

### Risk assessment

The European Public Assessment Reports (EPAR) noted that treatment-emergent adverse events (TEAEs) were higher in children and young people treatment with Guanfacine (GXR) compared with Atomoxetine or placebo, and considered that these differences between treatment groups were substantial and questioned the tolerability of Guanfacine compared to alternative treatments.

The most commonly reported adverse events in GXR groups include somnolence (40.6%), headache (27.4%), fatigue (18.1%), abdominal pain upper (12.0%), and sedation (10.2%). The adverse events occurred in 73.2% of people taking Guanfacine compared to Atomoxetine (55.4%) and Placebo (36.7%).
Discontinuation rates due to adverse events were higher in the Guanfacine group (10%) compared with Atomoxetine (4.5%) and placebo group (1.3%).

Serious adverse reactions commonly reported include hypotension (3.2%), weight increase (2.9%), bradycardia (1.5%) and syncope (uncommon 0.7%). The adverse reactions somnolence and sedation occurred predominately at the start of treatment and may typically last for 2-3 weeks and longer in some cases.

There are no controlled studies that directly compare the efficacy and safety of Guanfacine prolong-release with other active treatment for ADHD.

### Budget impact

**Estimated usage within England**

The manufacturer of guanfacine prolonged release estimates that uptake will be as a share of non-stimulants licensed for ADHD, of approximately 10%, 20% and 30% in years 1, 2 and 3 respectively. Prescription Cost Analysis data for 2014 shows that there were approximately 119,000 items for atomoxetine dispensed in primary care in England in 2014. As a percentage of these items, this equates to approximately 12,000 items of guanfacine prolonged-release in year 1, increasing to 36,000 in year 3 (estimate in primary care only).

### Funding

Guanfacine is not included in the NWL formulary, hence an agreement from the GP would need to be sought prior to transferring patients on guanfacine to primary care.

### Suggested place in therapy

In accordance with ADHD NICE guidelines, if medication is indicated then methylphenidate, atomoxetine and dexamfetamine within their licensed indications are recommended as options for the management of ADHD in children and young people. Choice of medication should be guided by comorbidities, adverse effects, specific issues that may affect compliance, the potential for drug diversion or misuse, and the preferences of the child or young person or their parent/carer.

Guanfacine/Intuniv® is licensed for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescent, 6 to 17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Guanfacine would provide an alternative licensed non-stimulant treatment option for management of ADHD in child and adolescents, with a different mechanism of action to the existing licensed treatment. The efficacy and safety profile of Guanfacine/Intuniv® has been demonstrated only in short-term controlled studies only, hence treatment should be reviewed on a regular basis.

The EPAR concluded that treatment with guanfacine resulted in clinically meaningful improvement in ADHD symptoms, although an effect on social functioning was not consistently shown. However, the safety profile is characterised by undesirable side effects which are common and limit tolerability. These include (orthostatic hypotension), bradycardia, sedation, fatigue and headache.

**Suggested place in therapy:**
- As per license in ages 6 to 17 years for whom stimulants are not suitable.
- Can only be initiated by a consultant
- Can only be prescribed if able to carry out all the monitoring in accordance with the license/Summary of Product Characteristics.
- Can only be prescribe if it is possible to continue prescribing within secondary care

If treatment with guanfacine is initiated it must be used as part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures. Pre-treatment screening is essential before Intuniv® is initiated. Ongoing physical health monitoring should be carried out during the first year, and thereafter in accordance with the manufacturer’s recommendations due to the increased incidence of serious adverse effects of guanfacine compared to atomoxetine.
Intuniv® is not licensed in adults with ADHD and so should not be used in this population. It is also not licensed for use in combination with stimulants.

Any suspected adverse effects associated with Intuniv® guanfacine prolonged-release tablets should be reported via the MHRA Yellow card adverse drug reactions reporting system online, www.mhra.gov.uk/yellowcard.

The manufacturer is also required to conduct a post-authorisation study in order to investigate the long-term safety (especially effects on neurocognitive function) of guanfacine, and so more safety data will become available in due course.

References

1. Intuniv® 1mg, 2mg, 3mg, 4mg prolonged-release tablets. Summary of Product Characteristics (SPC), Shire Pharmaceuticals Limited (last updated on 10/12/15); http://www.medicines.org.uk (assessed on 24/03/16).
3. Guanfacine, 1mg,2mg,3mg and 4mg prolonged-release tablets (Intuniv®), Scottish Medicines Consortium, SMC No.1123/16, 08January 2016; Published on 08 February 2016. https://www.scottishmedicines.org.uk (accessed on 17/02/16).

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