MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support

Guanfacine *(Intuniv®▼)*

For the treatment of attention deficit hyperactivity disorder (ADHD)

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of guanfacine for ADHD:

- The Summary of Product Characteristics (SPC) specifies that treatment with guanfacine must be initiated under the supervision of an appropriate specialist in childhood and/or behavioural disorders and that a baseline assessment is required.
- Ongoing monitoring is also required, and this may be best arranged through the use of an Essential Shared Care agreement.
- It was the opinion of the committee that additional factors to consider with this condition were:
  - The risk of increases in blood pressure and pulse rate on discontinuation of guanfacine, and the need to warn patient and/or carer not to stop treatment abruptly without downward titration and planned withdrawal.
  - The measures to be adopted when the child reaches 18 years of age and their care transfers to adult mental health services.

Strength of the evidence for efficacy

The strength of the evidence for efficacy for guanfacine was considered to be relatively weak. The trials evaluating the efficacy of guanfacine were of relatively short duration and there was no direct comparison with another standard treatment for this condition.

MTRAC considered guanfacine because it was a new licensed product that primary care prescribers may be asked to prescribe.

Description of technology

Guanfacine is non-stimulant medication licensed for the treatment of ADHD in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

The SPC[1] states that guanfacine must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures, and must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders. Before prescribing treatment, a baseline evaluation must be carried out 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 include blood pressure and heart rate, and a 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.

The recommended starting dose is 1 mg of guanfacine taken orally once daily. Dose titration over 3-4 weeks is necessary to minimise clinically significant adverse effects such as syncope (fainting), hypotension, bradycardia (slow heart rate), somnolence and sedation. Dose tapering is also required if treatment is to be stopped. See the SPC for full details.[1]

Background

ADHD is a common neurodevelopmental disorder in children and adolescents, and may persist into adulthood. The principal diagnostic features are inattention, hyperactivity and impulsive behaviour that is often disruptive and may become defiant and aggressive.

Current therapies include a combination of cognitive and behavioural therapy, and pharmacological intervention. Pharmacological intervention is by central nervous stimulants using methylphenidate or dexamfetamine, or atomoxetine.

Clinical evidence for efficacy and safety

Four RCTs[3-7] were identified that used a flexible-dose treatment regimen similar to the recommended dose titration tables included in the SPC for guanfacine. In all the trials, participants were required to have a diagnosis of ADHD of at least moderate severity, with an ADHD-Rating Scale (RS)-IV score* of 32 or more and a Clinical Global Impression-Severity (CGI-S) score of 4 or more. Flexible dosing was used, according to participant weight. Guanfacine was titrated to doses in the range 0.05 to 0.12 mg/kg/day or a daily dose of 1 to 4mg for participants aged 6 to 12 years and 1 to 7 mg for those aged 13 to 17 years; atomoxetine was used in one trial[3] at doses of 0.5 to 1.4 mg/kg/day in those under 70 kg, 40 to 80mg/day in participants over 70kg, increasing to 100mg if necessary. Participants were considered to be at optimal dose if they achieved a 30% or more reduction in ADHD-IV-RS score from baseline, and a CGI-I score of 1 or 2.

In one 10 to 13-week double-blind RCT[3], 338 participants (aged 6 to 17 years) with ADHD were treated with guanfacine, atomoxetine or placebo (at doses previously described). The primary outcome was the change in ADHD-RS-IV score from baseline to the end of the double-blind phase: week 10 for participants

Parents and clinicians independent rating of the severity of inattention (9 items), and hyperactivity/impulsivity (9 items symptoms). Items scored from 0 (no symptoms) to 3 (severe symptoms). Higher scores = more severe symptoms, the maximum is 54.

aged 6 to 12 years, and week 13 for participants aged 13 to 17 years. There were significantly greater improvements for guanfacine *vs*. placebo treatment (placebo-subtracted difference from baseline −8.9 points (95% confidence interval [CI] −11.9 to −5.8, p<0.001) and for the atomoxetine reference arm *vs*. placebo (placebo-subtracted score −3.8 points [95% CI −6.8 to −0.70, p=0.017]). The trial was not powered to test for the superiority of guanfacine over atomoxetine. Secondary end points included the change from baseline in the CGI-I rating scale (Clinician's Global Impression of change: 1, very much improved, or 2, much improved), and the learning and school domain, and family domain of WFIRS-P (Weiss Functional Impairment Rating Scale Parent Report). Sixty-eight percent of guanfacine-treated participants showed improvement in CGI-I at study end compared with 56% for atomoxetine and 44% for placebo ($p \leq 0.05$ for both treatments *vs*. placebo). The WFIRS-P scores also showed significantly greater improvements for guanfacine than placebo for both learning/school and family domains, whereas atomoxetine treatment showed significantly greater improvement in the learning/school domain only.

A second 13-week placebo-controlled RCT[5] evaluated guanfacine in 314 children aged 13 to 17 years of age. Similar inclusion criteria were used as for the previous 10-13 week trial (ADHD-RS score ≥ 28) but the average duration of ADHD was longer at 5.1 years in these participants, and about 70% had received stimulant medications. In this trial there was a significantly greater improvement in ADHD-RS-IV score for guanfacine compared with placebo. For guanfacine the mean change from baseline was −24.6 points *vs*. −18.5 points for placebo (p<0.001). More participants treated with guanfacine achieved a CGI-S score < 2 compared with placebo (50.6% and 36.1% respectively, p=0.01).

A shorter, 8-week double-blind, placebo-controlled RCT[4] evaluated morning or evening administration of guanfacine 1 to 4 mg daily in 333 children aged 6 to 12 years with ADHD. There was no significant difference in the change in ADHD-RS-IV scores from baseline for participants receiving either a morning or evening dose and all participants showed significant improvement over placebo (−19.8 points with guanfacine morning dosing, −20.1 with guanfacine evening dosing and −11.0 with placebo; p<0.001 for both guanfacine groups compared with placebo).

Finally, a 9-week double-blind, placebo-controlled trial[6] evaluated guanfacine 1 to 4mg daily in 217 children aged 6–12 years with ADHD and oppositional symptoms (unintentional aggression, anger, disobedience). The trial found significantly lower scores for guanfacine *vs*. placebo for the primary outcome, the change from baseline in scores using the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L), a rating of symptoms such as "loses temper" or "fights" judged on a scale from 0 to 3 (higher score represents more severe or frequent symptoms). The ADHD Rating Scale IV score was a secondary outcome and also showed significantly greater improvement with guanfacine *vs*. placebo (−23.8 points with guanfacine compared with −11.5 points with placebo, p<0.001).

Adverse events

One trial reported that treatment-emergent adverse events were reported in 77.2% (88/114) of people receiving guanfacine, compared with 67.9% (76/112) for atomoxetine and 65.8% (73/111) for placebo.[3] The most common adverse events with guanfacine treatment were somnolence, headache and fatigue[3,5]; with atomoxetine they were decrease in appetite, nausea and fatigue. In the same trial adverse events led to study discontinuation in 7.9% (9/114) of the guanfacine group, 4.5% (5/112) of the atomoxetine group and 0.9% (1/111) of the placebo group.[8] According to the SPC, the most frequently reported adverse reactions include somnolence (40.6%), headache (27.4%), fatigue (18.1%), upper abdominal pain (12.0%) and sedation (10.2%). Serious adverse reactions include hypotension (3.2%), weight increase (2.9%), bradycardia (1.5%) and syncope (0.7%). Somnolence and sedation occur predominantly at the start of treatment and may typically last for 2–3 weeks and longer in some cases.[1]

Considerations for cost impact

A 2015 systematic review[9] estimated the prevalence of ADHD to be about 7.2% of children from a broad range of geographical regions. Using 2011 census data, this equates to about 63,770 children (aged 5 to 17) in the West Midlands, of whom about 31,885 may have clinically significant impairment requiring intervention.

Costs for a years' treatment (excluding VAT; Prices: MIMS, Drug Tariff [Feb 2018]):

- Atomoxetine (Strattera®) 40mg – 80mg £692 - 1,384
- Dexamfetamine (Amfexa®▼) 10mg – 20mg £484 - 968
- Dexamfetamine (Generic) 10mg – 60mg £622 - 3,731
- Lisdexamfetamine (Elvanse®▼) 30mg - 70mg £759 - 1,084
- Methylphenidate (Generic) 10mg – 60mg £48 - 399
- Methylphenidate (Equasym XL®) 10mg – 60mg £304 - 852
- Guanfacine (Intuniv®▼) 1mg – 4 mg £730 - 993

References

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Keele University Centre for Medicines Optimisation

School of Pharmacy, Keele University, Keele, Staffordshire ST5 5BG Tel: 01782 733831 Email: mtrac@keele.ac.uk Web: www.mtrac.co.uk