# GUANFACINE

## ▼INTUNIV® FOR THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

## An old friend with much to demonstrate

dtbn
DRUG ASSESSMENT REPORT
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### Indications

Attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17 years when stimulant drugs are not appropriate, are not tolerated, or do not control symptoms adequately. It is used as part of a comprehensive treatment programme that typically involves psychological, educational, and social interventions.

### Mechanism of action

Non-stimulant selective alpha-2A adrenergic receptor agonist. Its mechanism of action in ADHD has not been established yet.

### Administration

Oral use: Starting dose: 1 mg/day either in the morning or evening. It should not be administered with high fat meals. The dose can be increased by a maximum of 1mg/week. The optimal dose ranges between 0.05 and 0.12 mg/kg/day. During dose titration, signs and symptoms of sleepiness, sedation, hypotension and bradycardia must be monitored on a weekly basis. Dose reduction must be progressive and do not exceed 1mg every 3-7 days.

### Efficacy

The four main trials on which authorization was based had a short duration (between 8 and 15 weeks). The primary endpoint was the improvement in the ADHD symptom score (ADHD-RS-IV) with respect to baseline score. ADHD-RS-IV is a 18-item scale with a maximum score of 54 points. Only one of the trials had a long duration (41 weeks), and its primary endpoint was the percentage of failures.

Also, patients —either naïve or previously treated— with any subtype of ADHD were included. The main trials revealed significant 6-to-10 point differences on the ADHD-RS-IV scale, as compared to placebo.

One of the trials assessed the effects of 1-4 mg/d of guanfacine taken for 12 weeks in children and 1-7 mg/d for 15 weeks in adolescents. The study included an active control arm with atomoxetine, although it was not designed for a direct comparison (table 1). Patients were considered to "respond" when a ≥ 30% reduction was achieved with respect to the baseline score on the ADHD-RS-IV scale, and score of 1 or 2 was obtained on the clinical global impressions scale (NCBI).[12]

The overall effect size among the different trials was 0.5 points, which is considered moderate and lower than that reported for methylphenidate. Results were less consistent in adolescents (13-17 years).

Results by subtype of ADHD (combined vs ADHD with prevalence of attention deficit) were statistically significant only for the combined subtype, which is suggestive that sedation plays a role in its efficacy.

### Safety

Sleepiness and sedation mainly occurred at the start of the treatment to progressively disappear. Response was dose-dependent. A trial revealed weight gain (from 20.0 to 21.8 in 24 months).

In total, 61.8% of patients in the long-term trial (41 weeks) discontinued guanfacine, 12.9% due to its adverse effects. Totally, 5.3% of patients taking a dose of 4mg withdrew from the study due to sedation and 1.3% due to hypotension.

### Special warnings and precautions for use[11]

It can cause fainting, hypotension and bradycardia. Prior to initiation of treatment, the patient must be tested for blood pressure and heart rate, family history of sudden cardiac / unexplained death, severe cardiac arrhythmias, usual medication, weight and height.

It is also recommended: 1. That the patient is warned about the high risk of somnolence. 2. That patient's response is monitored on a regular basis, with periods of rest (preferably during holidays). 3. That it is used with caution in patients with a history of QT-prolongation, use of medications that prolong the QT interval or in the presence of risk factors such as torsade de pointes. 4. In case of suicidal ideation, a possible change in the treatment programme must be considered.

Other regular checks include: 1. Heart rate, blood pressure, and symptoms of somnolence and sedation on a weekly basis during dose titration; every 3 months during the first year and thereafter every 6 months or more often in case a dose adjustment was required. 2. Height, weight and BMI every 3 months during the first year and thereafter every 6 months. 3. Blood pressure and heart rate in case the dose is reduced or the treatment is discontinued.

### Use in special situations[11]

No data are available on its impact on renal or liver failure. Pregnancy and lactation: Not recommended in women of childbearing age that do not use effective contraceptives. No data are


## ABSTRACT

**Guanfacine is a centrally-acting antihypertensive and a non-stimulant selective alpha-2A adrenergic receptor agonist.**

**It has not been proven to be superior or equal to any of the other drugs available for ADHD.**

**No data are available on its long-term safety profile of neurocognitive effects.**

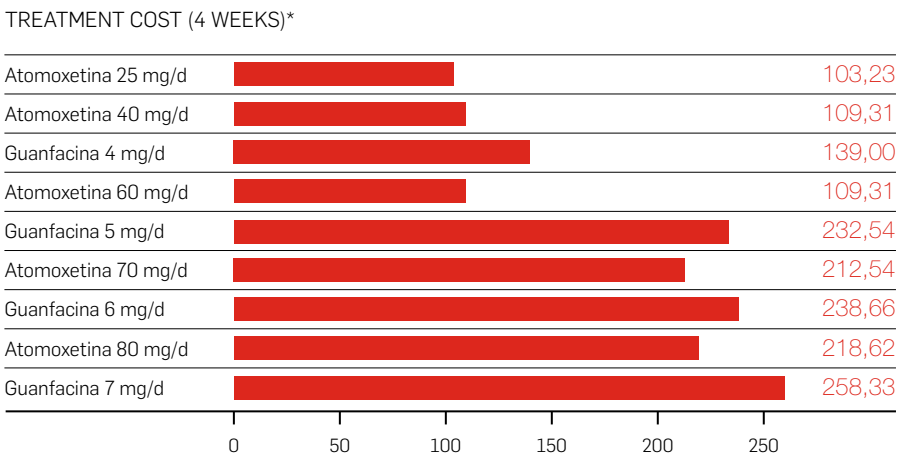
**Its most common side effects include: sleepiness, headache, fatigue, abdominal pain, sedation, and weight gain.**

**Worrying cardiovascular safety profile: hypotension, bradycardia, and fainting.**

**The cost per patient is higher than that of atomoxetine.**


## CLASSIFICATION

| | |
|---|---|
| 4 | IMPORTANT THERAPEUTIC INNOVATION |
| 3 | MODEST THERAPEUTIC INNOVATION |
| 2 | SOME ADDED VALUE IN SPECIFIC SITUATIONS |
| **1** | **NO THERAPEUTIC INNOVATION** |
| 0 | INSUFFICIENT EVIDENCE |




(*) Doses were compared according to patient's body weight.

**Table 1**[11]

| GROUP OF TREATMENT | N | IMPROVEMENT ON ADHD-RS-IV WITH RESPECT TO THE BASELINE SCORE (SD) | DIFFERENCE WITH PLACEBO (95% CI) EFFECT SIZE | RESPONDERS | DIFFERENCE WITH PLACEBO (95% CI) |
|---|---|---|---|---|---|
| Guanfacine | 114 | -23.9 (12.4) | -8.9 (-11.9 to -5.8) **0,7** | 64.30% | 21.9 % (9.2 to 34.7) |
| Atomoxetine | 112 | -18.6 (11.9) | -3.8 (-6.08 to -0.7) **0,3** | 55.40% | 13.0 % (0.0 to 26.0) |
| Placebo | 111 | -15.0 (13.1) | | 2-CRT | |

**Table 2. Adverse effects**[12]

| | GUANFACINE (n=2411) % | ATOMOXETINE (n=112) % | PLACEBO (n=973) % |
|---|---|---|---|
| Severe adverse effects (SAE*) | 2.0 | 0.0 | 0.8 |
| Somnolence | 39.4 | 16.1 | 9.7 |
| Sedation | 10.0 | 1.8 | 1.8 |
| Psychiatric | | | |
| Irritability, affectivity, anxiety, aggression and depression | 21.7 | 22.3 | 11.9 |
| Suicidal thoughts | 0.5 | 0.0 | 0.3 |
| Cardiovascular | | | |
| Fainting | 0.7 | 0.2 | 0.0 |
| Hypotension | 5.7 | 0.7 | 0.9 |
| Reduction of heart rate by ≤ 50 bpm | 10.8 | 1.0 | 0.8 |
| Prolongation of the QT ≥60ms | 14.0 | 0.0 | 1.2 |
| Drop-outs due to adverse effects | 10.8 | 4.5 | 1.3 |
| Due to central nervous system disorders | 5.4 | 1.8 | 0.4 |
| *Due to sleepiness* | 2.5 | 1.8 | 0.0 |
| *Due to psychiatric disorders* | 2.1 | 0.9 | 0.2 |
| Treatment discontinuation | 44.3 | 20.5 | 32 |

(*) Although this outcome is not provided in the IPT, it has been included in the table for being a standard outcome.

available on penetration into human milk and its effects on the baby.

## Interactions[11]

Antihypertensive: risk of hypotension and syncope. **Enzymes / enzyme inhibitors:** it is a substrate of CYP3A4 and its levels could be affected when used in combination with inducers (carbamazepine, phenytoin, phenobarbital, rifampicin, St. John's wort) or enzyme inhibitors (azole antifungals, macrolides, protease inhibitors). A dose adjustment might be required at initiation of the treatment programme, the use of the inductor or inhibitor might be suspended. The use of grapefruit juice should be avoided. **QT-interval prolongation drugs:** its use in combination is not recommended, as it reduces heart rate. **CNS depressants:** risk of worsening of somnolence. **Valproic acid:** it could increase valproate levels. Patients must be checked for toxicities.

## Place in therapeutics

ADHD remains a controversial disorder, as no objective criteria have been established yet. The main pharmacotherapy options are methylphenidate and atomoxetine. Methylphenidate has been proven to provide better rates of response and a faster effect. Therefore, it should be considered first-line therapy. When stimulators are contraindicated or not recommended (risk of substance abuse, some comorbidities or patient's preference for non-stimulators) atomoxetine is recommended. Lisdexamphetamine is only indicated when response to methylphenidate is inadequate, though evidence on its effectiveness is not solid. In patients with an inadequate response, diagnosis should be reconsidered and other disorders should be contemplated (mental retardation, depression, family problems). Treatment adherence should also be verified.

The effect of guanfacine in clinical practice is likely to be different from that obtained in trials, as:

- Patients with other psychiatric disorders were excluded in the trials —except for oppositional defiant disorder, low weight or overweight, hypertension or heart disorder with concomitant therapy for the CNS, convulsions or history of drug abuse.
- In light of the high rate of drop-outs, doubts have been raised on treatment adherence.
- No long-term studies have been performed to assess its safety in the long-term.
- No comparative studies have been performed with other drugs for ADHD.

## Conclusion

Guanfacine has not been proven to be superior or equal to any of the other drugs available for ADHD. No large comparative studies have been performed. Its effect vs placebo is moderate. There are doubts about its effectiveness in improving functionality and the observed benefits could be the consequence of its sedative effect. Its safety profile is characterized by sedation, hypotension, and syncope, weight gain and QT prolongation. No data are available on its long-term safety regarding its neurocognitive effects, which is relevant when the duration of treatment is long. Therefore, consistent studies are required to prove its effectiveness.

The reimbursed indication differs from the authorized one. Guanfacine has been reimbursed for ADHD in children and adolescents aged 6 to 17 years as an alternative when CNS stimulators (methylphenidate and amphetamines) and atomoxetine are no effective or are contraindicated.

## Presentations

Intuniv® (Shire Pharmaceuticals Ibérica) 28 coated tablets, 1 mg (€104.03), 2 mg (€113.21), 3 mg (€119.33) and 4 mg (€139).

## References

Based on the Evaluation report. Available at: https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-guanfacina-Intuniv-TDAH.pdf