ALPHA-2 ADRENERGIC AGONIST

Guanfacine

Intuniv (extended-release), Tenex (immediate-release)

Selective alpha-2A agonist used as extended-release for pediatric ADHD and as immediate-release for hypertension and off-label calming.

USUAL PEDIATRIC RANGE	HALF-LIFE	METABOLISM	ONSET
ER 1-7 mg/day PO once daily	~17-18 h (ER)	CYP3A4; ~50% renal unchanged	1-2 wks; BP effect immediate

No FDA boxed warning on the current US label.

INDICATIONS

- Intuniv extended-release is FDA-approved for ADHD in patients age 6 to 17 years, as monotherapy or as adjunct to stimulant therapy.
- Immediate-release guanfacine is FDA-approved only for hypertension in adults and carries no pediatric ADHD indication.
- Extended-release guanfacine is particularly useful for ADHD with prominent hyperactivity, impulsivity, oppositionality, or emotional dysregulation.
- Used off-label for tic disorders and Tourette syndrome, where alpha-2 agonists reduce tic severity and treat comorbid ADHD at once.
- Used off-label for adult ADHD, aggression and irritability in autism spectrum disorder, and hyperarousal symptoms of PTSD.
- Frequently added off-label to a morning stimulant to cover evening rebound, homework hours, and sleep-onset difficulty.

DOSING & TITRATION

- Intuniv: start **1 mg** PO once daily and adjust by no more than **1 mg per week**, targeting **0.05-0.12 mg/kg/day** as tolerated.
- Maximum studied dose is **4 mg/day** in children 6-12 years and **7 mg/day** in adolescents 13-17 years, including adjunctive use above 4 mg only rarely.
- Tablets must be swallowed whole, since crushing or chewing accelerates release and converts the product to an immediate-release exposure.
- Immediate-release guanfacine for hypertension in adults: **1 mg** PO at bedtime, increasing to 2 mg after 3-4 weeks, with a maximum of 3 mg/day.
- When discontinuing, taper by no more than **1 mg every 3 to 7 days** to avoid rebound hypertension, tachycardia, and agitation.
- Reduce the dose in significant renal or hepatic impairment, since clearance falls through both renal excretion and CYP3A4 metabolism.

MECHANISM OF ACTION

- Selective postsynaptic alpha-2A adrenergic receptor agonist, roughly 15 to 20 times more selective for alpha-2A than clonidine.
- Stimulating alpha-2A receptors on prefrontal cortical dendritic spines closes HCN channels and strengthens network connectivity.
- Improved prefrontal signal transmission enhances working memory, impulse control, and regulation of attention and emotion.
- Alpha-2A selectivity means less alpha-2B and alpha-2C activity, which translates into less sedation and hypotension than clonidine.
- The therapeutic effect is postsynaptic rather than presynaptic, so it does not depend on reducing central noradrenergic firing.

PHARMACOKINETICS

- Extended-release tablets reach Tmax at about 5 hours, roughly 3 hours later than immediate-release, with lower peak concentrations.
- Half-life is approximately 17-18 hours, supporting once-daily dosing in either the morning or the evening.
- Metabolized mainly by CYP3A4 to inactive metabolites, with about half of a dose excreted unchanged by the kidneys.
- High-fat meals raise extended-release exposure substantially, so the tablet should be taken consistently apart from such meals.
- Immediate-release and extended-release products are not interchangeable on a milligram basis and require independent titration.

ADVERSE EFFECTS

- Somnolence in about 38 percent, fatigue, sedation, headache, abdominal pain, and dry mouth are the leading adverse effects.
- Hypotension, bradycardia, dizziness, and syncope are dose related and are the usual limits on titration in slim younger children.
- Sedation typically peaks in the first 2-3 weeks and often improves with continued treatment or by moving the dose to bedtime.
- Abrupt discontinuation can cause rebound hypertension, tachycardia, headache, and nervousness, which is why a taper is required.
- Weight gain, irritability, and mild depressive symptoms are reported less commonly but occasionally lead to discontinuation.
- Overdose causes profound bradycardia, hypotension, and central nervous system depression and warrants cardiac monitoring.

MONITORING

- Baseline heart rate, blood pressure, and orthostatic vitals, repeated after each titration step and periodically during maintenance.
- Ask about daytime sedation, school performance, and sleepiness at each visit, since these determine dose timing more than dose size.
- Track ADHD symptoms with a validated scale at baseline and after 4-6 weeks at a stable dose before declaring nonresponse.
- Recheck cardiovascular status when other antihypertensives, sedatives, or CYP3A4 inhibitors are added to the regimen.
- Assess for missed doses, since interruptions of several days can produce rebound blood pressure elevation and irritability.

INTERACTIONS & CAUTIONS

- Strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, and ritonavir raise guanfacine exposure and generally warrant halving the dose.
- Strong CYP3A4 inducers such as carbamazepine, phenytoin, and rifampin lower exposure and may require doubling the dose.
- Additive sedation occurs with alcohol, benzodiazepines, opioids, antihistamines, and other central nervous system depressants.
- Additive hypotension and bradycardia occur with beta-blockers, calcium channel blockers, clonidine, and other antihypertensives.
- Valproate levels may rise when guanfacine is added, so check concentrations if the two are used together.

SPECIAL POPULATIONS

- Pregnancy: human data are limited and animal studies show no clear teratogenicity; use only when the benefit justifies the risk.
- Lactation: excretion into human milk is not characterized, so watch the breastfed infant for sedation and poor feeding.
- Pediatric: extended-release is approved from age 6; safety and effectiveness below age 6 have not been established.
- Geriatric: efficacy and safety of the extended-release product have not been established in older adults, who are prone to hypotension and falls.
- Renal or hepatic impairment: reduce the dose, since about half of guanfacine is cleared unchanged renally and the rest through CYP3A4.

PRESCRIBING PEARLS

- Never substitute immediate-release for extended-release milligram for milligram; retitrate from 1 mg.
- Sedation almost always fades by week 3; bedtime dosing usually rescues an otherwise useful trial.
- Stopping abruptly can cause rebound hypertension; taper by 1 mg every 3 to 7 days.

Verify against the current FDA label and your formulary before prescribing. Educational reference only.

References

Arnsten, A. F. T. (2010). The use of alpha-2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder. *Expert Review of Neurotherapeutics, 10*(10), 1595-1605. https://doi.org/10.1586/ern.10.133

Cortese, S. (2020). Pharmacologic treatment of attention deficit-hyperactivity disorder. *New England Journal of Medicine, 383*(11), 1050-1056. https://doi.org/10.1056/NEJMra1917069

Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A. J., Carucci, S., Atkinson, L. Z., Tessari, L., Banaschewski, T., Coghill, D., Hollis, C., Simonoff, E., Zuddas, A., Barbui, C., Purgato, M., Steinhausen, H. C., Shokraneh, F., Xia, J., & Cipriani, A. (2018). Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: A systematic review and network meta-analysis. *The Lancet Psychiatry, 5*(9), 727-738. https://doi.org/10.1016/S2215-0366(18)30269-4

National Institute for Health and Care Excellence. (2018). *Attention deficit hyperactivity disorder: Diagnosis and management* (NICE guideline NG87). https://www.nice.org.uk/guidance/ng87

National Institute of Diabetes and Digestive and Kidney Diseases. (2020). Guanfacine. In *LiverTox: Clinical and research information on drug-induced liver injury*. https://www.ncbi.nlm.nih.gov/books/NBK548586/

Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

Takeda Pharmaceuticals America. (2025). *Intuniv (guanfacine) extended-release tablets [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Wolraich, M. L., Hagan, J. F., Allan, C., Chan, E., Davison, D., Earls, M., Evans, S. W., Flinn, S. K., Froehlich, T., Frost, J., Holbrook, J. R., Lehmann, C. U., Lessin, H. R., Okechukwu, K., Pierce, K. L., Winner, J. D., & Zurhellen, W. (2019). Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics, 144*(4), e20192528. https://doi.org/10.1542/peds.2019-2528

NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.