GUANFACINE- guanfacine tablet, extended release
AvKARE, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
Guanfacine Extended-Release Tablets

These highlights do not include all the information needed to use guanfacine extended-release tablets safely and effectively. See full prescribing information for guanfacine extended-release tablets.

GUANFACINE extended-release tablets, for oral use

Initial U.S. Approval: 1986

RECENT MAJOR CHANGES

Dosage and Administration, Dose Selection (2.2) 2/2013

INDICATIONS AND USAGE

Guanfacine extended-release is a central alpha $_{2A}$-adrenergic receptor agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications (1).

DOSAGE AND ADMINISTRATION

- Recommended dose: 1 to 4 mg once daily in the morning or evening (2.2).
- Begin at a dose of 1 mg once daily and adjust in increments of no more than 1 mg/week (2.2).
- Do not crush, chew or break tablets before swallowing (2.1).
- Do not administer with high-fat meals, because of increased exposure (2.1).
- Do not substitute for immediate-release guanfacine tablets on a mg-per-mg basis, because of differing pharmacokinetic profiles (2.3).
- If switching from immediate-release guanfacine, discontinue that treatment and titrate with guanfacine extended-release as directed (2.3).
- Consider dosing on a mg/kg basis. Improvements observed starting at doses of 0.05 to 0.08 mg/kg once daily. Doses up to 0.12 mg/kg once daily may provide additional benefit (2.2).
- When discontinuing, taper the dose in decrements of no more than 1 mg every 3 to 7 days (2.5).

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 1 mg, 2 mg, 3 mg and 4 mg (3)

CONTRAINDICATIONS

History of hypersensitivity to guanfacine extended-release, its inactive ingredients, or other products containing guanfacine (4).

WARNINGS AND PRECAUTIONS

- Hypotension, bradycardia, and syncope: Use guanfacine extended-release with caution in patients at risk for hypotension, bradycardia, heart block, or syncope (e.g., those taking antihypertensives). Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Advise patients to avoid becoming dehydrated or overheated (5.1).
- Sedation and somnolence: Occur commonly with guanfacine extended-release. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to guanfacine extended-release (5.2).

ADVERSE REACTIONS

Most common adverse reactions (greater than or equal to 5% and at least twice placebo rate) in the monotherapy trials: somnolence, fatigue, nausea, lethargy, and hypotension (6). Most common adverse reactions (greater than or equal to 5% and at least twice placebo rate) in the adjunctive trial: somnolence, fatigue, insomnia, dizziness, and abdominal pain (6).
To report SUSPECTED ADVERSE REACTIONS, contact AvKARE, Inc. at 1-855-361-3993; email drugsafety@avkare.com; or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Strong CYP3A4 inhibitors (e.g., ketoconazole): Coadministration increases guanfacine exposure. Guanfacine dose should be limited to no more than 2 mg/day. When discontinuing CYP3A4 inhibitors, guanfacine dose should be doubled based on patient tolerability. The maximum dose should not exceed 4 mg/day (2.7 and 7).
- Strong CYP3A4 inducers (e.g., rifampin): Coadministration decreases guanfacine exposure. Guanfacine dose may be titrated up to 8 mg/day. When discontinuing CYP3A4 inducers, guanfacine dose should be decreased by half in 1 to 2

weeks based on patient tolerability. The maximum dose should not exceed 4 mg/day (2.7 and 7).

USE IN SPECIFIC POPULATIONS

Hepatic or Renal Impairment: dose reduction may be required in patients with clinically significant impairment of hepatic or renal function (8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 7/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

Guanfacine extended-release tablets are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications. The efficacy of guanfacine extended-release tabletswere studied for the treatment of ADHD in three controlled monotherapy clinical trials (up to 8 weeks in duration) and one controlled adjunctive trial with psychostimulants (8 weeks in duration) in children and adolescents ages 6 to 17 who met DSM-IV ® criteria for ADHD [see Clinical Studies (14)]. The effectiveness of guanfacine extended-release tablets for longer-term use (more than 8 weeks) has not been systematically evaluated in controlled trials.

2 DOSAGE & ADMINISTRATION

2.1 General Instruction for Use

Swallow tablets whole. Do not crush, chew, or break tablets because this will increase the rate of guanfacine release. Do not administer with high fat meals, due to increased exposure.

2.2 Dose Selection

Guanfacine extended-release tablets should be taken once daily, either in the morning or evening, at approximately same time each day. Begin at a dose of 1 mg/day, and adjust in increments of no more than 1 mg/week. Maintain the dose within the range of 1 mg to 4 mg once daily, depending on clinical response and tolerability, for both monotherapy and adjunctive therapy to a psychostimulant. Doses above 4 mg/day have not been systematically studied in controlled clinical studies [see Clinical Studies (14.1)].

Clinically relevant improvements were observed beginning at doses in the range 0.05 to 0.08 mg/kg once daily in both mono- and adjunctive therapy. Efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit.

In clinical trials, there were dose-related and exposure-related risks for several clinically significant adverse reactions (hypotension, bradycardia, sedative events). Thus, consideration should be given to dosing guanfacine extended-release on a mg/kg basis, in order to balance the exposure-related potential benefits and risks of treatment.

2.3 Switching from Immediate-Release Guanfacine to Guanfacine Extended-Release

If switching from immediate-release guanfacine, discontinue that treatment, and titrate with guanfacine extended-release following above recommended schedule.

Do not substitute for immediate-release guanfacine tablets on a milligram-per-milligram basis, because of differing pharmacokinetic profiles. Guanfacine extended-release has a delayed T_{max}, reduced C_{max} and lower bioavailability compared to those of the same dose of immediate-release guanfacine [see Clinical Pharmacology (12.3)].

2.4 Maintenance Treatment

It is generally agreed that pharmacological treatment of ADHD may be needed for extended period. The effectiveness of guanfacine extended-release for longer-term use (more than 9 weeks) has not been systematically evaluated in controlled trials. Therefore the physician electing to use guanfacine extended-release for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2.5 Discontinuation

Infrequent, transient elevations in blood pressure above original baseline (i.e., rebound) have been reported to occur upon abrupt discontinuation of guanfacine. To minimize these effects, the dose should generally be tapered in decrements of no more than 1 mg every 3 to 7 days.

2.6 Missed Doses

When reinitiating patients to the previous maintenance dose after two or more missed consecutive doses, physicians should consider titration based on patient tolerability.

2.7 Dose Adjustment with Concomitant Use of Strong CYP3A4 Inhibitors or Inducers

Dosage adjustments for guanfacine extended-release are recommended with concomitant use of strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole), or CYP3A4 inducers (e.g., avasimibe, carbamazepine, phenytoin, rifampin, and St. John's wort) (Table 1) [see Drug Interactions (7)].

Table 1: Dose Adjustments in Patients Taking Concomitant CYP3A4 Inhibitors or Inducers

	Scenarios		
Comedications	Initiate guanfacine extended-release when taking comedications	Continue guanfacine extended-release when adding a comedication	Stop a comedication when continuing guanfacine extended-release
Strong CYP3A4 Inhibitors	Guanfacine extended-release dose should be limited to 2 mg/day	Guanfacine extended-release dose should be decreased by half.	Guanfacine extended-release dose should be doubled based on patient tolerability. The maximum dose should not exceed 4 mg/day
Strong CYP3A4 Inducers	Guanfacine extended-release dose may be titrated up to 8 mg/day. Consider faster titration (e.g. in increments of 2 mg/week)	Consider increase guanfacine extended-release dose gradually in 1 to 2 weeks to 2 fold of the original dose based on patient tolerability.	Guanfacine extended-release dose should be decreased by half in 1 to 2 weeks based on patient tolerability. The maximum dose should not exceed 4 mg/day

3 DOSAGE FORMS & STRENGTHS

Guanfacine extended-release tablets are for oral administration and are available as follows:

1 mg - Each orange, round tablet debossed with  on one side and 850 on the other side contains guanfacine hydrochloride, USP equivalent to 1 mg of guanfacine base.

2 mg - Each orange, oval tablet debossed with  on one side and 851 on the other side contains guanfacine hydrochloride, USP equivalent to 2 mg of guanfacine base.

3 mg - Each yellow, round tablet debossed with  on one side and 853 on the other side contains guanfacine hydrochloride, USP equivalent to 3 mg of guanfacine base.

4 mg - Each yellow, oval tablet debossed with  on one side and 855 on the other side contains guanfacine hydrochloride, USP equivalent to 4 mg of guanfacine base.

4 CONTRAINDICATIONS

Patients with a history of hypersensitivity to guanfacine extended-release, its inactive ingredients [see Description (11)] or other products containing guanfacine should not take guanfacine extended-release.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension, Bradycardia, and Syncope

Treatment with guanfacine extended-release can cause dose-dependent decreases in blood pressure and heart rate. Decreases were less pronounced over time of treatment. Orthostatic hypotension and syncope have been reported [see Adverse Reactions (6.1)].

Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Use guanfacine extended-releasewith caution in patients with a history of hypotension, heart block, bradycardia, cardiovascular disease, or who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Use guanfacine extended-release with caution in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope. Advise patients to avoid becoming dehydrated or overheated.

5.2 Sedation and Somnolence

Somnolence and sedation were commonly reported adverse reactions in clinical studies [see Adverse Reactions (6.1)]. Before using guanfacine extended-release with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), consider the potential for additive sedative effects. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with guanfacine extended-release . Advise patients to avoid use with alcohol.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labelling:

- Hypotension, bradycardia, and syncope [see Warnings and Precautions (5.1)]
- Sedation and somnolence [see Warnings and Precautions (5.2)]

To report SUSPECTED ADVERSE REACTIONS contact AvKARE, Inc. at 1-855-361-3993; email drugsafety@avkare.com**; or FDA at 1-800-FDA-1088 or** www.fda.gov/medwatch**.**

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A total of 2,028 subjects have been exposed to guanfacine extended-releasewhile participating in clinical trials. This includes 1,533 patients from completed studies in children and adolescents, and 495 subjects in completed studies in adult healthy volunteers.

The mean duration of exposure of 446 patients that previously participated in two 2-year, open-label long-term studies was approximately 10 months.

Monotherapy Trials

Most Common Adverse Reactions - The most commonly observed adverse reactions (incidence greater than or equal to 5% and at least twice the rate for placebo) in the monotherapy trials (Studies 1 and 2) with guanfacine extended-releasewere: somnolence, fatigue, nausea, lethargy, and hypotension.

Adverse Reactions Leading to Discontinuation - Twelve percent (12%) of patients receiving guanfacine extended-release discontinued from the monotherapy clinical studies (Studies 1 and 2) due to adverse reactions, compared to 4% in the placebo group. The most common adverse reactions leading to

discontinuation of guanfacine extended-release-treated patients from the studies were somnolence/sedation (6%) and fatigue (2%). Less common adverse reactions leading to discontinuation (occurring in approximately 1% of patients) included: hypotension, headache, and dizziness.

Adjunctive Trial

Most Common Adverse Reactions - The most commonly observed adverse reactions (incidence greater than or equal to 5% and at least twice the rate for placebo) in the adjunctive trial with guanfacine extended-release were: somnolence, fatigue, insomnia, dizziness, and abdominal pain.

Adverse Reactions Leading to Discontinuation - In the adjunctive clinical study, 3% of patients receiving guanfacine extended-release discontinued due to adverse reactions, compared to 1% in the placebo group. Each adverse reaction leading to discontinuation occurred in less than 1% of guanfacine extended-release-treated patients.

Short Term Monotherapy Clinical Studies

Common Adverse Reactions - Two short-term, placebo-controlled, double-blind pivotal studies (Studies 1 and 2) were conducted in children and adolescents with ADHD, using fixed doses of guanfacine extended-release(1 mg, 2 mg, 3 mg, and 4 mg/day). The most commonly reported adverse reactions (occurring in greater than or equal to 2% of patients) that were considered drug-related and reported in a greater percentage of patients taking guanfacine extended-releasecompared to patients taking placebo are shown in Table 2. Adverse reactions that were dose-related include: somnolence/sedation, abdominal pain, dizziness, hypotension, dry mouth and constipation.

Table 2: Percentage of Patients Experiencing Common (Greater Than or Equal To 2%) Adverse Reactions in Short-Term Monotherapy Studies 1 and 2

Adverse Reaction Term	All Doses of Guanfacine Extended-Release (N=513)	Placebo (N=149)
Somnolence [a]	38%	12%
Headache	24%	19%
Fatigue	14%	3%
Abdominal pain [b]	11%	9%
Hypotension [c]	7%	3%
Nausea	6%	2%
Lethargy	6%	3%
Dizziness	6%	4%
Irritability	6%	4%
Decreased appetite	5%	3%
Dry mouth	4%	1%
Constipation	3%	1%

[a]: The somnolence term includes somnolence, sedation, and hypersomnia.

[b]: The abdominal pain term includes abdominal pain, abdominal pain upper, and abdominal pain lower.

[c]: The hypotension term includes hypotension, orthostatic hypotension, and decreased blood pressure.

In an 8-week, placebo-controlled study in children 6 to 12 years of age with ADHD in which guanfacine extended-release was dosed once (1 to 4 mg/day) in the morning or evening (Study 4), the safety profile was consistent with the once daily morning dosing of guanfacine extended-release.

Short Term Adjunctive Clinical Study

Common Adverse Reactions - A 8-week, placebo-controlled, double-blind, dose-optimized pivotal study (Study 3) was conducted in children and adolescents aged 6 to 17 years with a diagnosis of ADHD who

were identified as having a sub-optimal response to psychostimulants. Patients received guanfacine extended-release (1 mg, 2 mg, 3 mg, and 4 mg/day) or placebo, dosed in the morning or in the evening, in combination with their morning dose of psychostimulant. The most commonly reported adverse reactions (occurring in greater than or equal to 2% of patients in the overall guanfacine extended-release group) that were reported in a greater percentage of patients taking guanfacine extended-release compared to patients taking placebo are shown in Table 3.

Table 3: Percentage of Patients Experiencing Common (Greater Than or Equal To 2%) Adverse Reactions in Short-Term Adjunctive Study 3

Adverse Reaction Term	All Doses of Guanfacine Extended-Release	Placebo
	(N=302)[a]	(N=153)
Headache	21%	13%
Somnolence [b]	18%	7%
Insomnia [c]	12%	6%
Fatigue	10%	3%
Abdominal pain [d]	10%	3%
Dizziness	8%	4%
Decreased appetite	7%	4%
Nausea	5%	3%
Diarrhea	4%	1%
Hypotension [e]	3%	0%
Affect lability	2%	1%
Bradycardia	2%	0%
Constipation	2%	0%
Dry mouth	2%	0%

[a]: The morning and evening dose groups of guanfacine extended-release are combined.

[b]: The somnolence term includes somnolence, sedation, and hypersomnia.

[c]: The insomnia term includes insomnia, initial insomnia, and middle insomnia.

[d]: The abdominal pain term includes abdominal pain, abdominal pain upper, and abdominal pain lower.

[e]: The hypotension term includes hypotension, orthostatic hypotension, and decreased blood pressure.

Effects on Blood Pressure and Heart Rate

In the monotherapy pediatric, short-term, controlled trials (Studies 1 and 2), the maximum mean changes from baseline in systolic blood pressure, diastolic blood pressure, and pulse were -5 mmHg, -3 mmHg, and -6 bpm, respectively, for all dose groups combined (generally one week after reaching target doses of 1 mg/day, 2 mg/day, 3 mg/day or 4 mg/day). These changes were dose dependent. Decreases in blood pressure and heart rate were usually modest and asymptomatic; however, hypotension and bradycardia can occur. Hypotension was reported as an adverse reaction for 7% of the guanfacine extended-release group and 3% of the placebo group. This includes orthostatic hypotension, which was reported for 1% of the guanfacine extended-release group and none in the placebo group. In the adjunctive trial, hypotension (3%) and bradycardia (2%) were observed in patients treated with guanfacine extended-release as compared to none in the placebo group. In long-term, open label studies, (mean exposure of approximately 10 months), maximum decreases in systolic and diastolic blood pressure occurred in the first month of therapy. Decreases were less pronounced over time. Syncope occurred in 1% of pediatric subjects in the clinical program. The majority of these cases occurred in the long-term, open-label studies.

Other Adverse Reactions Observed in Clinical Studies

Table 4 includes additional adverse reactions observed in short-term, placebo-controlled and long-

term, open-label clinical studies not included elsewhere in section 6.1, listed by organ system.

Table 4: Other adverse reactions observed in clinical studies

Body System	Adverse Reaction
Cardiac	Atrioventricular block, sinus arrhythmia
Gastrointestinal	Dyspepsia, stomach discomfort, vomiting
General	Asthenia, chest pain
Immune System Disorders	Hypersensitivity
Investigations	Increased alanine amino transferase, increased weight
Nervous system	Convulsion
Psychiatric	Agitation, anxiety, depression, nightmare
Renal	Increased urinary frequency, enuresis
Respiratory	Asthma
Vascular	Hypertension, pallor

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of guanfacine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

An open-label postmarketing study involving 21,718 patients was conducted to assess the safety of guanfacine (as the hydrochloride) 1 mg/day given at bedtime for 28 days. Guanfacine was administered with or without other antihypertensive agents. Adverse events reported in the postmarketing study at an incidence greater than 1% included dry mouth, dizziness, somnolence, fatigue, headache and nausea. The most commonly reported adverse events in this study were the same as those observed in controlled clinical trials.

Less frequent, possibly guanfacine-related events observed in the postmarketing study and/or reported spontaneously, not included in section 6.1, include:

General: edema, malaise, tremor

Cardiovascular: palpitations, tachycardia

Central Nervous System: paresthesias, vertigo

Eye Disorders: blurred vision

Musculo-Skeletal System: arthralgia, leg cramps, leg pain, myalgia

Psychiatric: confusion, hallucinations

Reproductive System, Male: impotence

Respiratory System: dyspnea

Skin and Appendages: alopecia, dermatitis, exfoliative dermatitis, pruritus, rash

Special Senses: alterations in taste

7 DRUG INTERACTIONS

Guanfacine is primarily metabolized by CYP3A4 and its plasma concentrations can be affected significantly by CYP3A4 inhibitors or inducers (Figure 1). Dose adjustments are recommended [see Dosage and Administration (2.7)]. Guanfacine does not significantly affect exposures of methylphenidate and lisdexamfetamine when coadministered (Figure 2). Therefore, no dose adjustments in methylphenidate or lisdexamfetamine are necessary.

Figure 1: Impact of Other Drugs on the Pharmacokinetics (PK) of Guanfacine Extended-Release

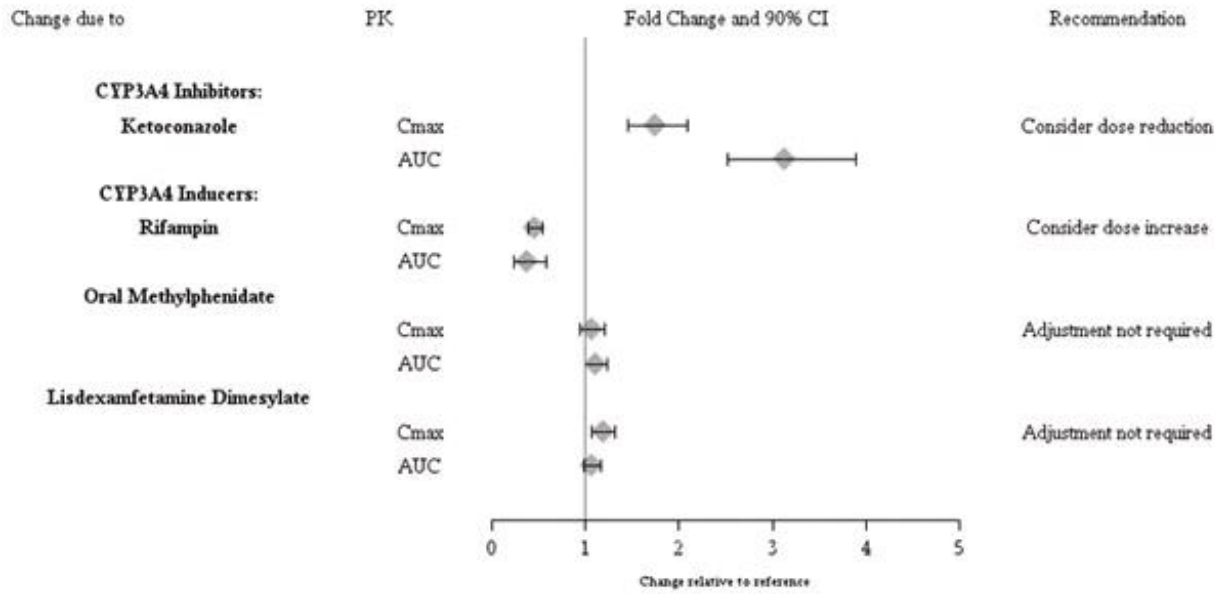
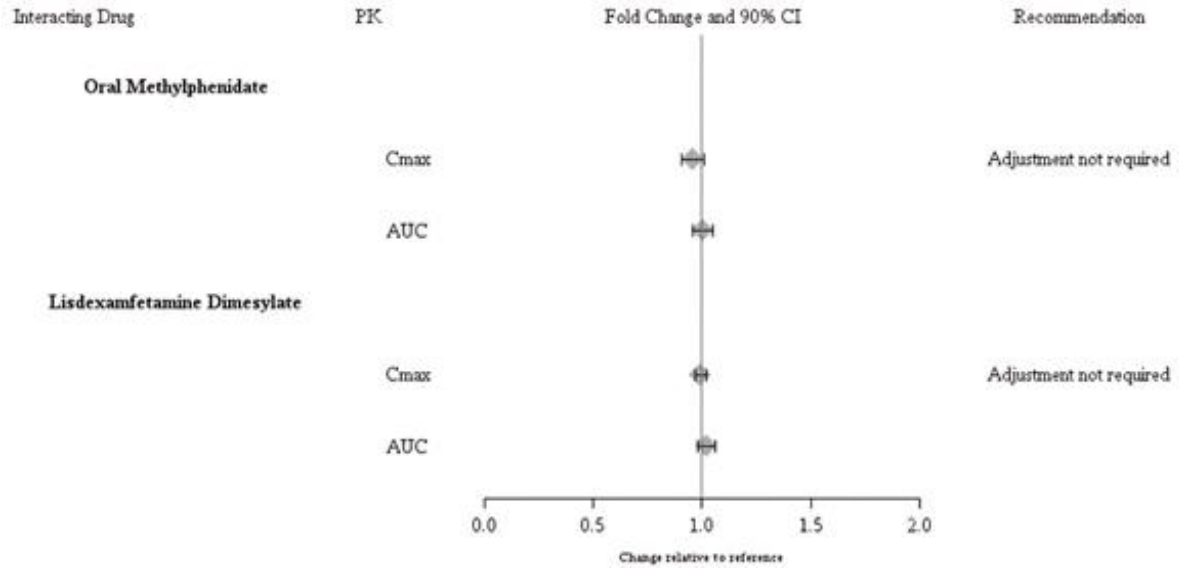


Figure 2: Impact of Guanfacine Extended-Release on the Pharmacokinetics (PK) of Other Drugs



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category B

Risk Summary

There are no adequate and well-controlled studies of guanfacine extended-release in pregnant women. No fetal harm was observed in rats and rabbits with administration of guanfacine at 6 and 4 times, respectively, the maximum recommended human dose. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Animal data

Reproduction studies conducted in rats have shown that guanfacine crosses the placenta. However, administration of guanfacine to rats and rabbits at 6 and 4 times, respectively, the maximum recommended human dose of 4 mg/day on a mg/m ^{2} basis resulted in no evidence of harm to the fetus. Higher doses (20 times the maximum recommended human dose in both rabbits and rats) were associated with reduced fetal survival and maternal toxicity.

8.3 Nursing Mothers

It is not known whether guanfacine is excreted in human milk; however, guanfacine is excreted in rat milk. Because many drugs are excreted in human milk, caution should be exercised when guanfacine extended-release is administered to a nursing woman. Observe human milk-fed infants for sedation and somnolence.

8.4 Pediatric Use

Safety and efficacy of guanfacine extended-release in pediatric patients less than 6 years of age have not been established

Animal Data

In studies in juvenile rats, guanfacine alone produced a slight delay in sexual maturation in males and females at 2 to 3 times the maximum recommended human dose (MRHD). Guanfacine in combination with methylphenidate produced a slight delay in sexual maturation and decreased growth as measured by a decrease in bone length in males at a dose of guanfacine comparable to the MRHD and a dose of methylphenidate approximately 4 times the MRHD.

In a study where juvenile rats were treated with guanfacine alone from 7 to 59 days of age, development was delayed as indicated by a slight delay in sexual maturation and decreased body weight gain in males at 2 mg/kg/day and in females at 3 mg/kg/day. The No Adverse Effect Level (NOAEL) for delayed sexual maturation was 1 mg/kg/day, which is equivalent to the MRHD of 4 mg/day, on a mg/m ^{2} basis. The effects on fertility were not evaluated in this study.

In a study where juvenile rats were treated with guanfacine in combination with methylphenidate from 7 to 59 days of age, a decrease in ulna bone length and a slight delay in sexual maturation were observed in males given 1 mg/kg/day of guanfacine in combination with 50 mg/kg/day of methylphenidate. The NOAELs for these findings were 0.3 mg/kg of guanfacine in combination with 16 mg/kg/day of methylphenidate, which are equivalent to 0.3 and 1.4 times the MRHD of 4 mg/day and 54 mg/day for guanfacine and methylphenidate, respectively, on a mg/m ^{2} basis. These findings were not observed with guanfacine alone at 1 mg/kg/day or methylphenidate alone at 50 mg/kg/day.

8.5 Geriatric Use

The safety and efficacy of guanfacine extended-release in geriatric patients have not been established.

8.6 Use in Patients with Renal or Hepatic Impairment

Renal Impairment

The impact of renal impairment on the pharmacokinetics of guanfacine in children was not assessed. In adult patients with impaired renal function, the cumulative urinary excretion of guanfacine and the renal clearance diminished as renal function decreased. In patients on hemodialysis, the dialysis clearance was about 15% of the total clearance. The low dialysis clearance suggests that the hepatic elimination (metabolism) increases as renal function decreases. It may be necessary to adjust the dose in patients with significant impairment of renal function.

Hepatic Impairment

The impact of hepatic impairment on PK of guanfacine in children was not assessed. Guanfacine in adults is cleared both by the liver and the kidney, and approximately 50% of the clearance of guanfacine

is hepatic. It may be necessary to adjust the dose in patients with significant impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Guanfacine extended-release is not a controlled substance and has no known potential for abuse or dependence.

10 OVERDOSAGE

Symptoms

Postmarketing reports of guanfacine overdosage indicate that hypotension, drowsiness, lethargy, and bradycardia have been observed following overdose. Initial hypertension may develop early and may be followed by hypotension. Similar symptoms have been described in voluntary reports to the American Association of Poison Control Center's National Poison Data System. Miosis of the pupils may be noted on examination. No fatal overdoses of guanfacine have been reported in published literature.

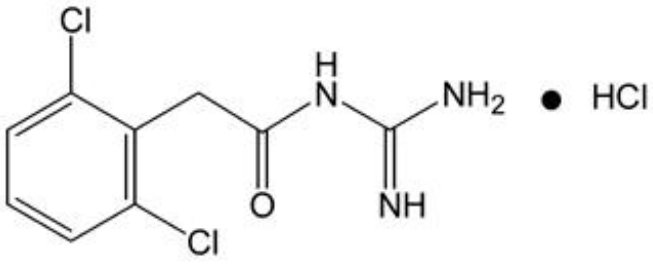
Treatment

Consult a Certified Poison Control Center by calling 1-800-222-1222 for up to date guidance and advice.

Management of guanfacine extended-release overdose should include monitoring for and the treatment of initial hypertension, if that occurs, as well as hypotension, bradycardia, lethargy and respiratory depression. Children and adolescents who develop lethargy should be observed for the development of more serious toxicity including coma, bradycardia and hypotension for up to 24 hours, due to the possibility of delayed onset hypotension.

11 DESCRIPTION

Guanfacine is a once-daily, extended-release formulation of guanfacine hydrochloride (HCl) in a matrix tablet formulation for oral administration only. The chemical designation is N-amidino-2-(2,6-dichlorophenyl) acetamide monohydrochloride. The molecular formula is $C_9H_9Cl_2N_3O$(HCl corresponding to a molecular weight of 282.55. The chemical structure is:



Guanfacine hydrochloride, USP is a white to off-white crystalline powder, sparingly soluble in water (approximately 1 mg/mL) and alcohol and slightly soluble in acetone. The only organic solvent in which it has relatively high solubility is methanol (greater than 30 mg/mL). Each tablet contains guanfacine hydrochloride, USP equivalent to 1 mg, 2 mg, 3 mg, or 4 mg of guanfacine base. The tablets also contain colloidal silicon dioxide, crospovidone, fumaric acid, glyceryl behenate, hydroxypropyl cellulose, hypromellose, lactose monohydrate, microcrystalline cellulose, and povidone. In addition, the 1 mg and 2 mg tablets contain FD&C Yellow #6 Aluminum Lake and the 3 mg and 4 mg tablets

contain D&C Yellow #10.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Guanfacine is a central alpha $_{2A}$-adrenergic receptor agonist. Guanfacine is not a central nervous system (CNS) stimulant. The mechanism of action of guanfacine in ADHD is not known.

12.2 Pharmacodynamics

Guanfacine is a selective central alpha $_{2A}$-adrenergic receptor agonist in that it has a 15 to 20 times higher affinity for this receptor subtype than for the alpha $_{2B}$ or alpha $_{2C}$ subtypes.

Guanfacine is a known antihypertensive agent. By stimulating central alpha $_{2A}$-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

Effects on Height, Weight, and Body Mass Index (BMI)

Patients taking guanfacine extended-release demonstrated similar growth compared to normative data. Patients taking guanfacine extended-release had a mean increase in weight of 0.5 kg (1 lb) compared to those receiving placebo over a comparative treatment period. Patients receiving guanfacine extended-release for at least 12 months in open-label studies gained an average of 8 kg (17 lbs) in weight and 8 cm (3 in) in height. The height, weight, and BMI percentile remained stable in patients at 12 months in the long-term studies compared to when they began receiving guanfacine extended-release.

Effect on ECG

The effect of two dose levels of immediate-release guanfacine (4 mg and 8 mg) on the QT interval was evaluated in a double-blind, randomized, placebo- and active-controlled, cross-over study in healthy adults. A dose-dependent decrease in heart rate was observed during the first 12 hours, at time of maximal concentrations. The mean change in heart rate was -13 bpm at 4 mg and -22 bpm at 8 mg. An apparent increase in mean QTc was observed for both doses. However, guanfacine does not appear to interfere with cardiac repolarization of the form associated with pro-arrhythmic drugs. This finding has no known clinical relevance.

12.3 Pharmacokinetics

Absorption and Distribution

Guanfacine is readily absorbed and approximately 70% bound to plasma proteins independent of drug concentration. After oral administration of guanfacine extended-releasethe time to peak plasma concentration is approximately 5 hours in children and adolescents with ADHD.

Immediate-release guanfacine and guanfacine extended-release have different pharmacokinetic characteristics; dose substitution on a milligram for milligram basis will result in differences in exposure.

A comparison across studies suggests that the C_{max} is 60% lower and $AUC_{0-\infty}$ 43% lower, respectively, for guanfacine extended-release compared to immediate-release guanfacine. Therefore, the relative bioavailability of guanfacine extended-release to immediate-release guanfacine is 58%. The mean pharmacokinetic parameters in adults following the administration of guanfacine extended-release 1 mg once daily and immediate-release guanfacine 1mg once daily are summarized in Table 5.

Table 5: Pharmacokinetic Parameters in Adults

Parameter	Guanfacine Extended-Release 1 mg once daily	Immediate-release guanfacine

	(n=52)	1 mg once daily (n=12)
C_{max} (ng/mL)	1.0 ± 0.3	2.5 ± 0.6
$AUC_{0-\infty}$ (ng.h/mL)	32 ± 9	56 ± 15
t_{max} (h)	6.0 (4.0 to 8.0)	3.0 (1.5 to 4.0)
$t_{½}$ (h)	18 ± 4	16 ± 3

Note: Values are mean +/- SD, except for t_{max} which is median (range)

Exposure to guanfacine was higher in children (ages 6 to 12) compared to adolescents (ages 13 to 17) and adults. After oral administration of multiple doses of guanfacine extended-release 4 mg, the C_{max} was 10 ng/mL compared to 7 ng/mL and the AUC was 162 ng h/mL compared to 116 ng h/mL in children (ages 6 to 12) and adolescents (ages 13 to 17), respectively. These differences are probably attributable to the lower body weight of children compared to adolescents and adults.

The pharmacokinetics were affected by intake of food when a single dose of guanfacine extended-release 4 mg was administered with a high-fat breakfast. The mean exposure increased (C_{max} ~75% and AUC ~40%) compared to dosing in a fasted state.

Dose Proportionality

Following administration of guanfacine extended-release in single doses of 1 mg, 2 mg, 3 mg, and 4 mg to adults, C_{max} and $AUC_{0-\infty}$ of guanfacine were proportional to dose.

Metabolism and Elimination

In vitro studies with human liver microsomes and recombinant CYP's demonstrated that guanfacine was primarily metabolized by CYP3A4. In pooled human hepatic microsomes, guanfacine did not inhibit the activities of the major cytochrome P450 isoenzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5). Guanfacine is a substrate of CYP3A4/5 and exposure is affected by CYP3A4/5 inducers/inhibitors.

Renal and Hepatic Impairment

The impact of renal impairment on PK of guanfacine in children was not assessed [see Use in Specific Populations (8.6)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenic effect of guanfacine was observed in studies of 78 weeks in mice or 102 weeks in rats at doses up to 6 to 7 times the maximum recommended human dose of 4 mg/day on a mg/ m^2 basis.

Mutagenesis

Guanfacine was not genotoxic in a variety of test models, including the Ames test and an *in vitro* chromosomal aberration test; however, a marginal increase in numerical aberrations (polyploidy) was observed in the latter study.

Impairment of Fertility

No adverse effects were observed in fertility studies in male and female rats at doses up to 30 times the maximum recommended human dose on a mg/ m^2 basis.

14 CLINICAL STUDIES

14.1 Safety and Efficacy Studies

The efficacy of guanfacine extended-release in the treatment of ADHD was established in 3 placebo-controlled monotherapy trials (Studies 1, 2 and 4) and in 1 placebo-controlled adjunctive trial with psychostimulants (Study 3) in pediatric population. Studies 1, 2, and 3 were conducted in children and adolescents ages 6 to 17 and Study 4 was conducted in children ages 6 to 12 years.

Studies 1 and 2: Fixed-dose Guanfacine Extended-Release Monotherapy

Study 1 was a double-blind, placebo-controlled, parallel-group, fixed dose study, in which efficacy of once daily dosing with guanfacine extended-release (2 mg, 3 mg and 4 mg) was evaluated for 5 weeks (n=345). Study 2 was a double-blind, placebo-controlled, parallel-group, fixed-dose study, in which efficacy of once daily dosing with guanfacine extended-release (1 mg, 2 mg, 3 mg and 4 mg) was evaluated for 6 weeks (n=324). In both studies, randomized subjects in 2 mg, 3 mg and 4 mg dose groups were titrated to their target fixed dose, and continued on the same dose until a dose tapering phase started The lowest dose of 1 mg used in Study 2 was assigned only to patients less than 50 kg (110 lbs). Patients who weighed less than 25 kg (55 lbs) were not included in either study.

Signs and symptoms of ADHD were evaluated on a once weekly basis using the clinician administered and scored ADHD Rating Scale (ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the change from baseline to endpoint in ADHD-RS-IV total scores. Endpoint was defined as the last post-randomization treatment week for which a valid score was obtained prior to dose tapering (up to Week 5 in Study 1 and up to Week 6 in Study 2).

The mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for guanfacine extended-release compared to placebo for Studies 1 and 2. Placebo-adjusted changes from baseline were statistically significant for each of the 2 mg, 3 mg, and 4 mg guanfacine extended-release randomized treatment groups in both studies, as well as the 1 mg guanfacine extended-release treatment group (for patients 55 to 110 lbs) that was included only in Study 2 (see Table 6).

Dose-responsive efficacy was evident, particularly when data were examined on a weight-adjusted (mg/kg) basis. When evaluated over the dose range of 0.01 to 0.17 mg/kg/day, clinically relevant improvements were observed beginning at doses in the range 0.05 to 0.08 mg/kg/day. Doses up to 0.12 mg/kg/day were shown to provide additional benefit.

Controlled, monotherapy long-term efficacy studies (greater than 9 weeks) have not been conducted.

In the monotherapy trials (Studies 1 and 2), subgroup analyses were performed to identify any differences in response based on gender or age (6 to 12 vs. 13 to 17). Analyses of the primary outcome did not suggest any differential responsiveness on the basis of gender. Analyses by age revealed a statistically significant treatment effect only in the 6 to 12 age subgroup. Due to the relatively small proportion of adolescent patients (ages 13 to 17) enrolled into these studies (approximately 25%), these data may not be sufficient to demonstrate efficacy in the adolescent patients. In these studies, patients were randomized to a fixed dose of guanfacine extended-release rather than optimized by body weight. Therefore, some adolescent patients were randomized to a dose that might have resulted in relatively lower plasma guanfacine concentrations compared to the younger patients. Over half (55%) of the adolescent patients received doses of 0.01 to 0.04mg/kg. In studies in which systematic pharmacokinetic data were obtained, there was a strong inverse correlation between body weight and plasma guanfacine concentrations.

Table 6: Fixed dose Studies

Study	**Primary Efficacy Measure**	**Treatment Group**			
		Placebo	**Guanfacine Extended-Release 1 mg**	**Guanfacine Extended-Release 2 mg**	**Guanfacine Extended-Release 3 mg**	**Guanfacine Extended-Release 4 mg**
(Age Range)						

	Mean Baseline (SD)	38.1 (9.34)	--	36.1 (9.99)	36.8 (8.72)	38.4 (9.21)
1 (6 to 17 years)	LS Mean Change from Baseline (SE)	-8.5 (1.42)	--	-15.9 (1.37)	-16.0 (1.38)	-18.5 (1.39)
	LS Mean Difference from Placebo (95% CI)	--	--	-7.4 [a] (-11.3, -3.5)	-7.5 [a] (-11.4, -3.6)	-10.0 [a] (-13.9, -6.1)
	Mean Baseline (SD)	39.3 (8.85)	41.7 (7.81)	39.9 (8.74)	39.1 (9.22)	40.6 (8.57)
	LS Mean Change from Baseline (SE)	-12.7 (1.60)	-19.4 (1.69)	-18.1 (1.60)	-20.0 (1.64)	-20.6 (1.60)
2 (6 to 17 years)	LS Mean Difference from Placebo (95% CI)	--	-6.8 [a] (-11.3, -2.2)	-5.4 [a] (-9.9, -0.9)	-7.3 [a] (-11.8, -2.8)	-7.9 [a] (-12.3, -3.4)

LS Mean: least-square mean; SD: standard deviation; SE: standard error; 95% CI (unadjusted)
[a] Doses were shown to be statistically significantly superior to placebo.

Study 3: Flexible-dose Guanfacine Extended-Release as Adjunctive Therapy to Psychostimulants

Study 3 was a double-blind, randomized, placebo-controlled, dose-optimization study, in which efficacy of once daily optimized dosing (morning or evening) with guanfacine extended-release (1mg, 2mg, 3mg and 4mg), when co-administered with psychostimulants, was evaluated for 8 weeks, in children and adolescents aged 6 to 17 years with a diagnosis of ADHD, with a sub-optimal response to stimulants (n=455). Subjects were started at the 1 mg guanfacine extended-release dose level and were titrated weekly over a 5-week dose-optimization period to an optimal guanfacine extended-release dose not to exceed 4 mg/day based on tolerability and clinical response. The dose was then maintained for a 3-week dose maintenance period before entry to 1 week of dose tapering. Subjects took guanfacine extended-release either in the morning or the evening while maintaining their current dose of psychostimulant treatment given each morning. Allowable psychostimulants in the study were ADDERALL XR ®, VYVANSE ® , CONCERTA ®, FOCALIN XR ®, RITALIN LA ®, METADATE CD ® or FDA-approved generic equivalents.

Symptoms of ADHD were evaluated on a weekly basis by clinicians using the ADHD Rating Scale

(ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the change from baseline to endpoint in ADHD-RS-IV total scores. Endpoint was defined as the last post-randomization treatment week prior to dose tapering for which a valid score was obtained (up to Week 8).

Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for guanfacine extended-release given in combination with a psychostimulant compared to placebo given with a psychostimulant for Study 3, for both morning and evening guanfacine extended-release dosing (see Table 7). Nearly two-thirds (64.2%) of subjects reached optimal doses in the 0.05 to 0.12 mg/kg/day range.

Study 4: Flexible-dose Guanfacine Extended-Release Monotherapy

Study 4 was a double-blind, randomized, placebo-controlled, dose-optimization study, in which efficacy of once daily dosing (morning or evening) with guanfacine extended-release (1mg, 2mg, 3mg, and 4mg) was evaluated for 8 weeks in children aged 6 to 12 years (n=340).

Signs and symptoms of ADHD were evaluated on a once weekly basis using the clinician administered and scored ADHD Rating Scale (ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the change from baseline score at endpoint on the ADHD-RS-IV total scores. Endpoint was defined as the last post-randomization treatment week for which a valid score was obtained prior to dose tapering (up to Week 8).

Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for guanfacine extended-release compared to placebo in both AM and PM dosing groups of guanfacine extended-release (see Table 7).

Table 7: Flexible-Dose studies

Study (Age Range)		**Treatment Group**		
		Placebo	**Guanfacine Extended-Release 1mg to 4mg**	
			AM	**PM**
3 [a] (6 to 17 years)	Mean Baseline (SD)	37.7 (7.75)	37.6 (8.13)	37.0 (7.65)
	LS Mean Change from Baseline (SE)	-15.9 (0.96)	-20.3 (0.97)	-21.2 (0.97)
	LS Mean Difference from Placebo (95% CI)	--	-4.5 [b] (-7.5, -1.4)	-5.3 [b] (-8.3, -2.3)
4 (6 to 12 years)	Mean Baseline (SD)	42.9 (6.21)	41.7 (6.39)	41.6 (6.66)
	LS Mean Change from Baseline (SE)	-10.6 (1.20)	-20.0 (1.23)	-20.4 (1.19)
	LS Mean	--	-9.4 [b]	-9.8 [b]

Difference from Placebo (95% CI)	(-12.8, -6.0)	(-13.1, -6.4)

LS Mean: least-square mean; SD: standard deviation; SE: standard error; 95% CI (unadjusted)

[a] Treatment was given in combination with a psychostimulant.

[b] Doses were shown to be statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

Guanfacine extended-release tablets are available as follows:

1 mg - Each orange, round tablet debossed with  on one side and 850 on the other side contains guanfacine hydrochloride, USP equivalent to 1 mg of guanfacine base. Tablets are supplied in bottles of 100 (NDC 42291-324-01).

2 mg - Each orange, oval tablet debossed with  on one side and 851 on the other side contains guanfacine hydrochloride, USP equivalent to 2 mg of guanfacine base. Tablets are supplied in bottles of 100 (NDC 42291-325-01).

3 mg - Each yellow, round tablet debossed with  on one side and 853 on the other side contains guanfacine hydrochloride, USP equivalent to 3 mg of guanfacine base. Tablets are supplied in bottles of 100 (NDC 42291-326-01).

4 mg - Each yellow, oval tablet debossed with  on one side and 855 on the other side contains guanfacine hydrochloride, USP equivalent to 4 mg of guanfacine base. Tablets are supplied in bottles of 100 (NDC 42291-327-01).

Store at 25(C (77(F); excursions permitted to 15 to 30(C (59 to 86(F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Dosing and Administration

Instruct patients to swallow guanfacine extended-release tablets whole with water, milk or other liquid. Tablets should not be crushed, chewed or broken prior to administration because this may increase the rate of release of the active drug. Patients should not take guanfacine extended-release together with a high-fat meal, since this can raise blood levels of guanfacine extended-release. Instruct the parent or caregiver to supervise the child or adolescent taking guanfacine extended-release and to keep the bottle of tablets out of reach of children.

Instruct patients on how to properly taper the medication, if the physician decides to discontinue treatment. [see Dosage and Administration (2.5)].

Adverse Reactions

Advise patients that sedation can occur, particularly early in treatment or with dose increases. Caution against operating heavy equipment or driving until they know how they respond to treatment with guanfacine extended-release [see Warnings and Precautions (5.2)]. Headache and abdominal pain can also occur. If any of these symptoms persist, or other symptoms occur, the patient should be advised to discuss the symptoms with the physician.

Advise patients to avoid becoming dehydrated or overheated which may potentially increase the risks of

hypotension and syncope. [see Warnings and Precautions (5.1)], Advise patients to avoid use with alcohol.

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Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 06/14
AV 06/15 (P)

PATIENT INFORMATION

Guanfacine (GWAHN-fa-seen) Extended-Release Tablets

Rx Only

Read the Patient Information that comes with guanfacine extended-release before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is guanfacine extended-release?

Guanfacine extended-release is a prescription medicine used to treat the symptoms of attention deficit/hyperactivity disorder (ADHD).

Guanfacine extended-release is not a central nervous system (CNS) stimulant.

What should I tell my doctor before taking guanfacine extended-release?

Before you take guanfacine extended-release, tell your doctor if you:

- have heart problems or a low heart rate
- have fainted
- have low blood pressure
- have liver or kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if guanfacine extended-release will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if guanfacine extended-release passes into your breast milk. Talk to your doctor about the best way to feed your baby while taking guanfacine extended-release.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Guanfacine extended-release may affect the way other medicines work, and other medicines may affect how guanfacine extended-release works.

Especially tell your doctor if you take:

- ketoconazole
- medicines that can affect enzyme metabolism
- high blood pressure medicine
- sedatives
- benzodiazepines
- barbiturates
- antipsychotics

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take guanfacine extended-release?

- Take guanfacine extended-release exactly as your doctor tells you.
- Your doctor may change your dose. Do not change your dose of guanfacine extended-release without talking to your doctor.
- Do not stop taking guanfacine extended-release without talking to your doctor.
- Guanfacine extended-release should be taken 1 time a day in the morning or in the evening, either alone or in combination with an ADHD stimulant medication that your doctor may prescribe. Your doctor will tell you when to take guanfacine extended-release and when to take your ADHD stimulant medication.
- Guanfacine extended-release tablets should be swallowed whole with a small amount of water, milk, or other liquid.
- Do not crush, chew, or break guanfacine extended-release tablets. Tell your doctor if you cannot swallow guanfacine extended-release tablets whole.
- Do not take guanfacine extended-release with a high-fat meal.
- Your doctor will check your blood pressure and heart rate while you take guanfacine extended-release.
- If you take too much guanfacine extended-release, call your local Poison Control Center or go to the nearest emergency room right away.

What should I avoid while taking guanfacine extended-release?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how guanfacine extended-release affects you. Guanfacine extended-release can slow your thinking and motor skills.
- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking guanfacine extended-release until you talk with your doctor. Guanfacine extended-release taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

What are the possible side effects of guanfacine extended-release?

Guanfacine extended-release may cause serious side effects including:

- low blood pressure
- low heart rate
- fainting
- sleepiness

Get medical help right away, if you have any of the symptoms listed above.

The most common side effects of guanfacine extended-release include:

• sleepiness	• nausea
• tiredness	• stomach pain
• trouble sleeping	• dizziness
• low blood pressure	

Tell the doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of guanfacine extended-release. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store guanfacine extended-release tablets?

- Store guanfacine extended-release tablets between 59°F to 86°F (15°C to 30°C)

Keep guanfacine extended-release tablets and all medicines out of the reach of children.

General Information about guanfacine extended-release tablets

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use guanfacine extended-release for a condition for which it was not prescribed. Do not give guanfacine extended-release to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about guanfacine extended-release. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about guanfacine extended-release that is written for health professionals.

For more information, you can call AvKARE, Inc. at 1-855-361-3993.

What are the ingredients in guanfacine extended-release tablets?

Active ingredient: guanfacine hydrochloride, USP

Inactive ingredients: colloidal silicon dioxide, crospovidone, fumaric acid, glyceryl behenate, hydroxypropyl cellulose, hypromellose, lactose monohydrate, microcrystalline cellulose, and povidone. In addition, the 1 mg and 2 mg tablets contain FD&C Yellow #6 Aluminum Lake and the 3 mg and 4 mg tablets contain D&C Yellow #10.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 06/14
AV 06/15 (P)

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

AvKARE

NDC 42291-324-01

Guanfacine Extended-Release Tablets

1 mg

Tablets should not be crushed, chewed or broken before swallowing.

100 Tablets Rx Only

PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

Each Extended-Release Tablet Contains:
Guanfacine Hydrochloride, USP equivalent to 1 mg of Guanfacine base.

Contains FD&C Yellow #6 Aluminum Lake as a color additive.

Usual Dosage: See accompanying product information for complete dosage recommendations.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25º (77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature].

Keep out of the reach of children.

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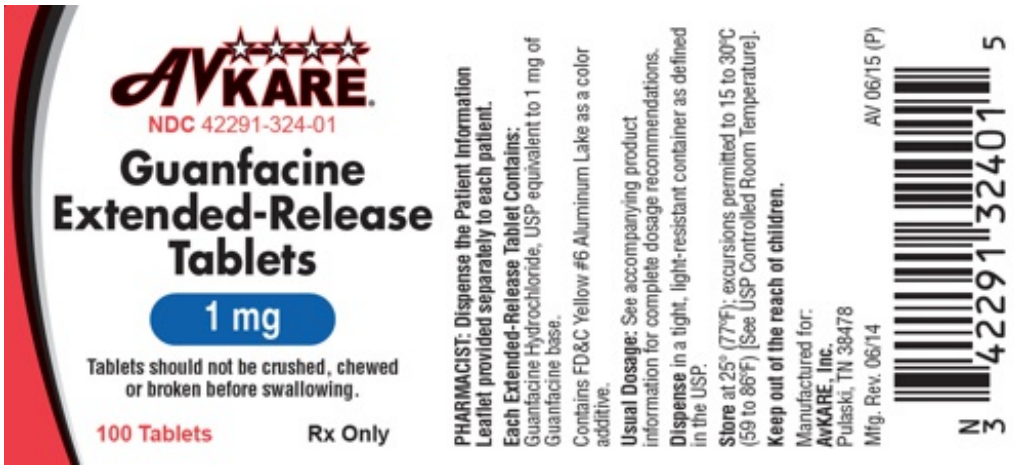

AvKARE

NDC 42291-325-01

Guanfacine Extended-Release Tablets

2 mg

Tablets should not be crushed, chewed or broken before swallowing.

100 Tablets Rx Only

PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

Each Extended-Release Tablet Contains:
Guanfacine Hydrochloride, USP equivalent to 2 mg of Guanfacine base.

Contains FD&C Yellow #6 Aluminum Lake as a color additive.

Usual Dosage: See accompanying product information for complete dosage recommendations.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25º (77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature].

Keep out of the reach of children.

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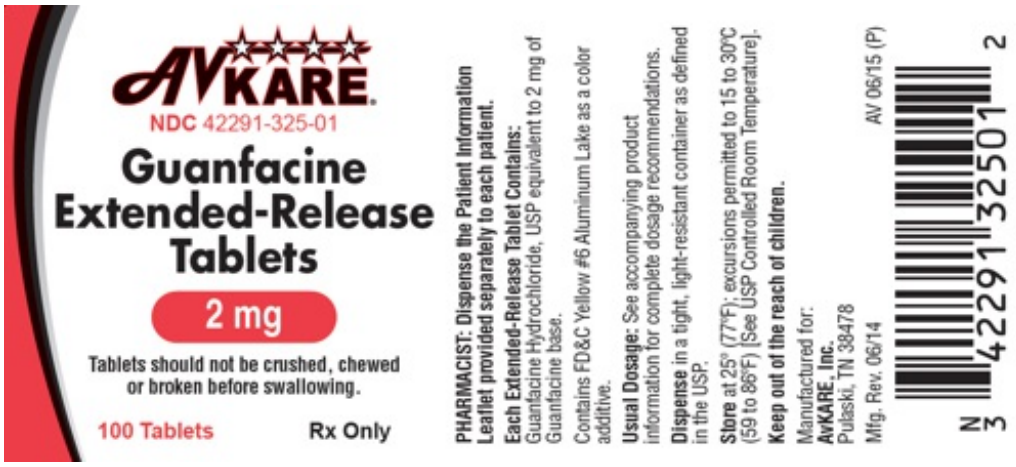

AvKARE

NDC 42291-326-01

Guanfacine Extended-Release Tablets

3 mg

Tablets should not be crushed, chewed or broken before swallowing.

100 Tablets Rx Only

PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

Each Extended-Release Tablet Contains:
Guanfacine Hydrochloride, USP equivalent to 3 mg of Guanfacine base.

Usual Dosage: See accompanying product information for complete dosage recommendations.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25º (77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature].

Keep out of the reach of children.

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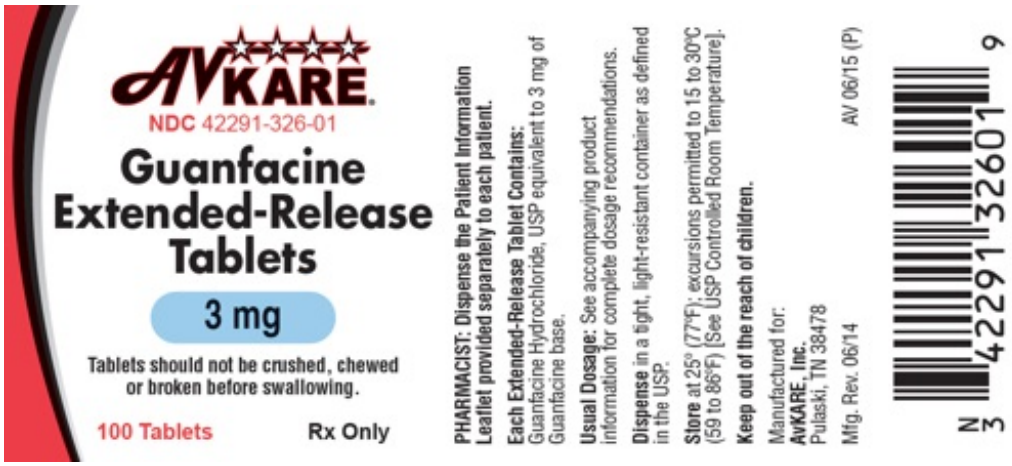

AvKARE

NDC 42291-327-01

Guanfacine Extended-Release Tablets

4 mg

Tablets should not be crushed, chewed or broken before swallowing.

100 Tablets Rx Only

PHARMACIST: Dispense the Patient Information Leaflet provided separately to each patient.

Each Extended-Release Tablet Contains:
Guanfacine Hydrochloride, USP equivalent to 4 mg of Guanfacine base.

Contains FD&C Yellow #6 Aluminum Lake as a color additive.

Usual Dosage: See accompanying product information for complete dosage recommendations.

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25º (77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [See USP Controlled Room Temperature].

Keep out of the reach of children.

Manufactured for:
AvKARE, Inc.
Pulaski, TN 38478

Mfg. Rev. 06/14 AV 06/15 (P)

N3 42291 32701 6

GUANFACINE

guanfacine tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42291-324(NDC:0228-2850)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
GUANFACINE HYDROCHLORIDE (UNII: PML56A160O) (GUANFACINE - UNII:30OMY4G3MK)	GUANFACINE	1 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
FUMARIC ACID (UNII: 88XHZ13131)	
GLYCERYL BEHENATE/EICOSADIOATE (UNII: 73CJJ317SR)	
HYDROXYPROPYL CELLULOSE (TYPE G) (UNII: VQ8ZWO78F6)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONES (UNII: FZ989GH94E)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics			
Color	orange	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	850
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-324-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	07/07/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200881	07/07/2015	

GUANFACINE

guanfacine tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:42291-325(NDC:0228-2851)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
GUANFACINE HYDROCHLORIDE (UNII: PML56A160O) (GUANFACINE - UNII:30OMY4G3MK)	GUANFACINE	2 mg

Inactive Ingredients	
Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
FUMARIC ACID (UNII: 88XHZ13131)	
GLYCERYL BEHENATE/EICOSADIOATE (UNII: 73CJJ317SR)	
HYDROXYPROPYL CELLULOSE (TYPE G) (UNII: VQ8ZWO78F6)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONES (UNII: FZ989GH94E)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics			
Color	orange	Score	no score
Shape	OVAL	Size	12mm
Flavor		Imprint Code	851
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date

1	NDC:42291-325-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	07/07/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200881	07/07/2015	

GUANFACINE

guanfacine tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42291-326(NDC:0228-2853)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GUANFACINE HYDROCHLORIDE (UNII: PML56A160O) (GUANFACINE - UNII:30OMY4G3MK)	GUANFACINE	3 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
FUMARIC ACID (UNII: 88XHZ13131)	
GLYCERYL BEHENATE/EICOSADIOATE (UNII: 73CJJ317SR)	
HYDROXYPROPYL CELLULOSE (TYPE G) (UNII: VQ8ZWO78F6)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONES (UNII: FZ989GH94E)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	yellow	**Score**	no score
Shape	ROUND	**Size**	9mm
Flavor		**Imprint Code**	853
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-326-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	07/07/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA200881	07/07/2015	

GUANFACINE

guanfacine tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:42291-327(NDC:0228-2855)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GUANFACINE HYDROCHLORIDE (UNII: PML56A160O) (GUANFACINE - UNII:30OMY4G3MK)	GUANFACINE	4 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (UNII: 68401960MK)	
FUMARIC ACID (UNII: 88XHZ13131)	
GLYCERYL BEHENATE/EICOSADIOATE (UNII: 73CJJ317SR)	
HYDROXYPROPYL CELLULOSE (TYPE G) (UNII: VQ8ZWO78F6)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONES (UNII: FZ989GH94E)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	

Product Characteristics

Color	yellow	**Score**	no score
Shape	OVAL	**Size**	12mm
Flavor		**Imprint Code**	855
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42291-327-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	07/07/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

ANDA	ANDA200881	07/07/2015	

Labeler - AvKARE, Inc. (796560394)

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