PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-GUANFACINE XR

Guanfacine Extended-Release Tablets

Extended-release tablets; 1 mg, 2 mg, 3 mg, 4 mg of guanfacine (as guanfacine hydrochloride), Oral

Apotex Standard

Selective Alpha$_{2A}$-Adrenergic Receptor Agonist

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RECENT MAJOR LABEL CHANGES

Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Pediatrics (6 -17 years of age)
APO-GUANFACINE XR (guanfacine extended-release tablets) is indicated as monotherapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents aged 6 to 17 years.

APO-GUANFACINE XR is also indicated as adjunctive therapy to psychostimulants for the treatment of ADHD in children and adolescents, aged 6 to 17 years, with a sub-optimal response to psychostimulants.

A diagnosis of ADHD (DSM-IV-TR®) implies the presence of hyperactive-impulsive and/or inattentive symptoms that cause impairment and were present before the age of 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work), and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, “on the go”, excessive talking, blurting answers, can’t wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations
The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program
APO-GUANFACINE XR is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational/vocational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in a patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis.
Appropriate educational/vocational placement is essential for patients with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment will depend upon the physician's assessment of the chronicity and severity of the child's symptoms and on the level of functional impairment.

Long-term Use
The effectiveness of APO-GUANFACINE XR for long-term use, i.e., for more than 9 weeks in 6-12 year olds and more than 15 weeks in 13-17 year olds, has not been systematically evaluated in controlled monotherapy trials, nor has it been systematically evaluated in controlled adjunctive trials for longer than 9 weeks in 6-17 year olds. Therefore the physician electing to use APO-GUANFACINE XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

1.1 Pediatrics

Pediatrics (<6 years of age): The safety and efficacy of APO-GUANFACINE XR in children less than 6 years of age have not been studied.

1.2 Adults

Adults (>18 years of age): APO-GUANFACINE XR has not been systematically studied in and is therefore not indicated for use in adults (over 18 years of age).

1.3 Geriatrics

APO-GUANFACINE XR has not been systematically studied in and is therefore not indicated for use in geriatrics.

2 CONTRAINDICATIONS

APO-GUANFACINE XR is contraindicated in patients with a history of hypersensitivity to this drug, to any ingredient in the formulation, to any other product containing guanfacine, or component of the container. For a complete listing, see **Dosage Forms, Strengths, Composition and Packaging**.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The tablets should not be administered with high-fat meals, due to increased exposure (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Do not substitute for immediate-release guanfacine tablets on a milligram for milligram basis, because of differing pharmacokinetic profiles. APO-GUANFACINE XR has a delayed T_{max}, reduced C_{max} and lower bioavailability compared to those of the same dose of immediate-release guanfacine.

The safety and efficacy of APO-GUANFACINE XR in pediatric patients less than 25 kg/55 lbs in weight have not been studied.

Heart rate and blood pressure should be monitored at baseline, after dose adjustments, periodically during treatment and following drug discontinuation (see **WARNINGS AND PRECAUTIONS, Cardiovascular**, and **WARNINGS AND PRECAUTIONS, Monitoring and**

Laboratory Tests).

Advise patients that sedation can occur, particularly early in treatment or with dose increases. If sedation is judged to be clinically concerning or persistent, a dose decrease or discontinuation should be considered (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Discontinuation).

4.2 Recommended Dose and Dosage Adjustment

4.2.1 Children (6-17 years old)

The recommended starting dose for both APO-GUANFACINE XR monotherapy and adjunct therapy to psychostimulants is 1 mg, taken orally once a day (morning or evening).

The dose should be adjusted, depending on clinical response and tolerability, in increments of no more than 1 mg per week up to a maximum daily dose of 4 mg (6-12 years) or 7 mg (13-17 years), for monotherapy and up to a maximum daily dose of 4 mg for adjunctive therapy to psychostimulants.

In monotherapy clinical trials, there were dose-related and exposure-related risks for several clinically significant adverse reactions (hypotension, bradycardia, sedative events). To balance the exposure-related potential benefits and risks, the recommended dose range, depending on clinical response and tolerability for guanfacine extended-release tablet, is 0.05-0.12 mg/kg/day (total daily dose 1-7 mg) (Table 1).

Table 1 - Recommended Target Dose Range for guanfacine extended-release tablet monotherapy* (depending on clinical response and tolerability)

Weight	Target dose range (0.05 - 0.12 mg/kg/day)
25.0-33.9 kg	2-3 mg/day
34.0-41.4 kg	2-4 mg/day
41.5-49.4 kg	3-5 mg/day
49.5-58.4 kg	3-6 mg/day
≥58.5 kg	4-7 mg/day
***Doses above 4 mg/day have not been evaluated in children (ages 6-12 years) and doses above 7 mg/day have not been evaluated in adolescents (ages 13-17 years)**	

In the adjunctive clinical trial which evaluated guanfacine extended-release tablet treatment added to psychostimulants, the majority of subjects reached their optimal doses in the 0.05-0.12 mg/kg/day range. Doses above 4 mg/day have not been studied in adjunctive trials.

4.2.2 Renal Impairment

The impact of renal impairment on the pharmacokinetics of guanfacine in children and adolescents, 6-17 years old, 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 (see WARNINGS AND PRECAUTIONS, Renal).

4.2.3 Hepatic Impairment

The impact of hepatic impairment on the pharmacokinetics of guanfacine in children and adolescents, 6-17 years old, 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 (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

4.2.4 Patients treated with CYP3A4/5 inhibitors /inducers

CYP3A4/5 inhibitors and inducers have been shown to have a significant effect on the pharmacokinetics of guanfacine when co-administered (see **DRUG INTERACTIONS, Drug-Drug Interactions**). 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). In the case of concomitant use of strong and moderate CYP3A inhibitors, an initial 50% reduction of the guanfacine dose is recommended. Further individualized dose titration may then be needed. If guanfacine is combined with strong enzyme inducers, a retitration to increase the dose up to a maximum daily dose 7 mg, may be considered if needed. If the inducing treatment is ended, retitration to reduce the guanfacine dose is recommended during the following weeks.

4.2.5 Discontinuation

Patients/caregivers should be instructed not to discontinue APO-GUANFACINE XR without consulting their physician. The total daily dose should be tapered in decrements of no more than 1 mg every 3 to 7 days to minimize the risk of an increase in blood pressure upon discontinuation (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Elevated Blood Pressure and Heart Rate Upon Discontinuation** and **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Elevations in blood pressure and heart rate above original baseline (i.e., rebound) have been reported to occur upon discontinuation of guanfacine hydrochloride monotherapy. Patients should be monitored during dose downward titration and following APO-GUANFACINE XR discontinuation until blood pressure and heart rate have returned to baseline (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

Caution is warranted when ending APO-GUANFACINE XR treatments in patients on the adjunctive to psychostimulant therapy while maintaining psychostimulant treatments. Use caution when prescribing drugs that can elevate blood pressure and heart rate immediately following APO-GUANFACINE XR discontinuation (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

4.3 Administration

APO-GUANFACINE XR is an extended-release tablet and should be dosed once daily. Tablets should not be crushed, chewed or broken before swallowing because this will increase the rate of guanfacine release.

The initial starting dose for APO-GUANFACINE XR as an adjunctive therapy with psychostimulants is 1 mg, taken orally once a day; evening dosing may be considered (see **CLINICAL TRIALS**).

See also **DOSAGE AND ADMINISTRATION, Dosing Considerations** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

4.5 Missed Dose

If two or more consecutive doses are missed, re-titration is recommended based on the patient's tolerability to APO-GUANFACINE XR (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Discontinuation**).

5 OVERDOSAGE

Signs and symptoms of overdose may include hypotension, bradycardia, lethargy, and respiratory depression. Initial hypertension may develop early and may be followed by hypotension. Management of APO-GUANFACINE XR overdose should include monitoring for and the treatment of these signs and symptoms. ECG monitoring is recommended. 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 of these symptoms.

Treatment of overdose may include gastric lavage if it is performed soon after ingestion. Activated charcoal may be useful in limiting the absorption. Guanfacine is not dialyzable in clinically significant amounts (2.4%).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet / 1 mg, 2 mg, 3 mg, 4 mg [milligrams] / guanfacine as guanfacine hydrochloride	Anhydrous Lactose, colloidal silicon dioxide, fumaric acid, hypromellose, indigotine aluminium lake, magnesium stearate, yellow ferric oxide

APO-GUANFACINE XR tablets 1 mg: White to off-white, round, biconvex tablet. Engraved "APO" on one side, "GU1" on the other side. Bottles of 100.

APO-GUANFACINE XR tablets 2 mg: White to off-white, oval shaped, biconvex tablet. Engraved "APO" on one side, "GUA 2" on the other side. Bottles of 100.

APO-GUANFACINE XR tablets 3 mg: Green, round, biconvex tablet. Engraved "APO" on one side, "GU3" on the other side. Bottles of 100.

APO-GUANFACINE XR tablets 4 mg: Green, oval shaped, biconvex tablet. Engraved "APO" on one side, "GUA 4" on the other side. Bottles of 100.

7 WARNINGS AND PRECAUTIONS

General

Somnolence and Sedation

Sedative events, especially during initial use, were commonly reported adverse reactions in clinical trials. In two 8-and 9-week monotherapy trial (Studies 1 and 2) in 6-17 year olds, sedative events reported as adverse reactions were 38% for guanfacine hydrochloride vs. 12% for placebo and in a separate monotherapy trial in adolescents (Study 3), were 54% for guanfacine hydrochloride vs. 23% for placebo. In an adjunctive trial (Study 4) in 6-17 year olds, sedative events reported as adverse events were 18% for guanfacine hydrochloride vs. 7% for placebo. Guanfacine hydrochloride should be dosed based on clinical response and tolerability. Advise patients that sedation can occur, particularly early in treatment or with dose increases. If sedation is judged to be clinically concerning or persistent, a dose decrease or discontinuation should be considered. Before APO-GUANFACINE XR is used with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered.

Patients should avoid use with alcohol (see **DRUG INTERACTIONS, Drug-Drug Interactions - CNS Depressant Drugs** and **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Cardiovascular

Hypotension, Bradycardia and Syncope

APO-GUANFACINE XR can cause syncope and dose-dependent decreases in heart rate and blood pressure (systolic and diastolic) (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**, **Effects on Blood Pressure and Heart Rate** and **ACTION AND CLINICIAL PHARMACOLOGY, Cardiovascular Safety: Effects on Heart Rate and QT Interval**). In pediatric (6-17 year olds), short-term (8-9 weeks), controlled monotherapy trials (Studies 1 and 2), the maximum mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate were decreases of 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). In the adolescent controlled monotherapy trial (Study 3), the maximum mean change from baseline in systolic blood pressure, diastolic blood pressure and heart rate were decreases of 5 mmHg, 4 mmHg, and 6 bpm for all dose groups combined. Decreases in blood pressure and heart rate were usually asymptomatic; however, hypotension and bradycardia can occur. 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. The majority of syncope cases occurred in the long term, open-label studies.

In a 9-week controlled adjunctive trial, the maximum mean changes from baseline in supine systolic blood pressure, diastolic blood pressure, and heart rate were decreases of 4 mmHg, 3 mmHg, and 9 bpm, respectively, between weeks 3 and 5 of the study. Decreases in blood pressure and heart rate were usually asymptomatic; however, hypotension and bradycardia can occur.

Measurements of heart rate and blood pressure should be performed prior to initiating therapy, following dose adjustments, periodically during treatment and following drug discontinuation. Observe caution if using APO-GUANFACINE XR in patients who have a history of hypotension, heart block, bradycardia, or other cardiovascular disease (e.g., arrhythmia, sick sinus syndrome, ischemic heart disease, congestive heart failure, or congenital long QT syndrome), as APO-GUANFACINE XR can decrease blood pressure and heart rate. Caution is advised when treating patients with APO-GUANFACINE XR who have a history

of syncope or a condition that may predispose them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration.

Given the effect on blood pressure and heart rate, caution is advised when treating patients with APO-GUANFACINE XR who are being treated concomitantly with antihypertensives or other drugs that reduce blood pressure or heart rate, QT prolonging drugs, and drugs that increase the risk of syncope (see **DRUG INTERACTIONS, Drug-Drug Interactions - Heart Rate Lowering Drugs**, and **DRUG INTERACTIONS, Overview - QT Prolonging Drugs**, and **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**, **Effects on Heart Rate and QT Interval**).

Patients/caregivers should be advised that patients should avoid becoming dehydrated or overheated.

Elevated Blood Pressure and Heart Rate Upon Discontinuation
Patients/caregivers should be instructed not to discontinue APO-GUANFACINE XR without consulting their physician since elevations in blood pressure and heart rate above original baseline (i.e., rebound) have been reported. In post-marketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation of guanfacine extended-release tablet.

To minimize the risk of an increase in blood pressure upon discontinuation, the total daily dose of APO-GUANFACINE XR should be tapered in decrements of no more than 1 mg every 3 to 7 days. Patients should be monitored during dose downward titration and following APO-GUANFACINE XR discontinuation until blood pressure and heart rate have returned to baseline (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**, **Discontinuation**).
Patients/caregivers should be informed about the risk of persistent hypertension following discontinuation, how to identify signs and symptoms (e.g. headaches, feeling confused, nervousness, agitation, and tremors) and to seek immediate medical care.

In randomized controlled monotherapy trials, increases of up to 10 mmHg persisted in a few individuals at approximately 30 days post-dose and were not considered serious. In a 26-week long-term randomized withdrawal study in children and adolescents, increases in mean systolic and diastolic blood pressure, of approximately 3 mmHg and 1mmHg respectively were observed upon discontinuation of guanfacine hydrochloride. Increases up to 36 mmHg above normal baseline persisted in a few individuals, which ranged between 3 and 26 weeks post-dose upon discontinuation of guanfacine hydrochloride. More than 90% of patients' blood pressure measurements remained within normal limits (i.e. less than the 95th percentile based on age, sex and stature). Mean increases in pulse of approximately 1.5 bpm were observed at approximately 2 weeks after the last dose of guanfacine hydrochloride and then decreased to baseline 4 weeks later. A few cases of hypertension were observed in this study, however, the increases in blood pressure and pulse were generally not considered serious or associated with adverse events. One pediatric case had a serious event of withdrawal hypertension despite downward dose titration associated with the adverse event of vomiting (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**, **Effects on Blood Pressure and Heart Rate** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Because of the psychostimulant potential for increasing blood pressure and heart rate, there is a theoretical increased risk of rebound or a risk of greater rebound when discontinuing APO-GUANFACINE XR treatments in patients on adjunctive therapy. Caution is warranted if a

patient stops APO-GUANFACINE XR while maintaining its psychostimulant therapy. Use caution when prescribing drugs that can elevate blood pressure and heart rate immediately following APO-GUANFACINE XR discontinuation (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

QTc Interval

QTc increase (placebo-adjusted mean change from baseline approximately 5 msec) has been observed in patients aged 6-17 years with ADHD receiving therapeutic doses of guanfacine hydrochloride at steady-state. In clinical trials of guanfacine hydrochloride in ADHD patients, there were no reports of torsade de pointes. Given the effect of guanfacine hydrochloride on cardiac electrophysiology, consider this observation in clinical decisions to prescribe guanfacine hydrochloride to patients with a known history of QT prolongation, risk factors for torsades de pointes (e.g. heart block, bradycardia, hypokalemia) or patients who are taking medications known to prolong the QT interval (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**, **Effects on Heart Rate and QT Interval** and **DRUG INTERACTIONS, Overview - QT Prolonging Drugs**).

Dependence/Tolerance

APO-GUANFACINE XR is not a controlled substance or a stimulant drug. APO-GUANFACINE XR has not been studied for abuse or dependence potential.

Driving and Operating Machinery

Patients should avoid performing tasks which may require special attention, such as riding a bike, driving/operating machinery or doing other dangerous activities, until they are reasonably certain that treatment with APO-GUANFACINE XR does not adversely affect them (see **WARNINGS AND PRECAUTIONS, General, Somnolence and Sedation**).

Hepatic/Biliary/Pancreatic

The impact of hepatic impairment on the pharmacokinetics of guanfacine in children and adolescents, 6-17 years old, was not assessed. Because guanfacine is metabolized primarily by cytochrome P450 (CYP)3A4, diminished CYP3A4 activity as a result of hepatic impairment would be expected to increase guanfacine exposure. It may be necessary to adjust the dose in patients with significant impairment of hepatic function (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**, **Hepatic Impairment**).

Monitoring and Laboratory Tests

Routine laboratory tests are not required. Heart rate and blood pressure should be monitored at baseline, after dose adjustments, periodically during treatment and following drug discontinuation. Withdrawal hypertension may occur within days after cessation of therapy; however, symptoms can occur up to 1-2 weeks after withdrawal of APO-GUANFACINE XR (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**, **Discontinuation**).

Particular caution should be observed in patients with pre-existing hypertension or hypotension, bradycardia, heart block, or other cardiovascular disease (e.g., arrhythmia, sick sinus syndrome, ischemic heart disease, congestive heart failure, or congenital long QT syndrome) or a history of syncope (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Patients/caregivers should be advised that patients should avoid dehydration or becoming overheated. Advise patients that sedation can occur, particularly early in treatment or with dose increases. If sedation is judged to be clinically concerning or persistent, a dose decrease or discontinuation should be considered.

Psychiatric

Pre-existing Psychosis
Administration of medications for ADHD may exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Screening Patients for Bipolar Disorder
Particular care should be taken in treating ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with APO-GUANFACINE XR , patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can occur with guanfacine use at usual doses. If such symptoms occur, consideration should be given to a possible causal role of guanfacine, and discontinuation of treatment should be considered.

Aggression
Aggressive behaviour or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that guanfacine causes aggressive behaviour or hostility, patients beginning treatment of ADHD should be monitored for the appearance of, or worsening of, aggressive behaviour or hostility.

Suicidal Behaviour and Ideation
There have been post-marketing reports of suicide-related events in patients treated with ADHD drugs, including cases of ideation, attempts, and very rarely, completed suicide. The mechanism of this risk is not known. ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour. Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behaviour, including at dose initiation/optimization and drug discontinuation. Patients should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional. Patients with emergent suicidal ideation and behaviour should be evaluated immediately. The physician should initiate appropriate treatment of the underlying psychiatric condition and consider a possible change in the ADHD treatment regimen.

Renal

The impact of renal impairment on the pharmacokinetics of guanfacine in children and adolescents, 6-17 years old, was not assessed. In adult patients with impaired renal function, the cumulative urinary excretion of immediate-release 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. 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 renal function (see **Dosage and Administration, Recommended Dose and Dosage Adjustment, Renal Impairment**).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of guanfacine hydrochloride in pregnant women. Non-clinical studies showed fetal and maternal toxicity (see **Non Clinical Toxicology**). APO-GUANFACINE XR should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the fetus.

7.1.2 Breast-feeding

There are no clinical data on the use of guanfacine hydrochloride in women who are breast feeding. In non-clinical studies, guanfacine was excreted into rat milk. It is not known if guanfacine would also be excreted into human milk. Use caution when APO-GUANFACINE XRis administered to a woman who is breast feeding.

7.1.3 Pediatrics

The safety and efficacy of APO-GUANFACINE XR in children less than 6 years of age have not been studied.

Effects on Growth
Pediatric patients aged 6-17 years taking guanfacine hydrochloride demonstrated similar growth compared to normative data. Patients taking guanfacine hydrochloride had a mean increase in weight of 0.5 kg (1 pound) compared to those receiving placebo over a comparative treatment period. Patients receiving guanfacine hydrochloride for at least 12 months in open-label studies gained an average of 8 kg (17 pounds) in weight and 8 cm (3 inches) 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 APO-GUANFACINE XR. Nevertheless, height, weight and BMI should be routinely monitored.

7.1.4 Adults

The safety and efficacy of APO-GUANFACINE XR in adults have not been studied.

7.1.5 Geriatrics

The safety and efficacy of APO-GUANFACINE XR in geriatrics have not been studied.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Short-Term Monotherapy Trials (children/adolescents aged 6-17 years)
The two forced-dose clinical trials (Studies 1 and 2) with guanfacine hydrochloride alone, one 8-week and one 9-week, were randomized, multi-center, double-blind, parallel-group, placebo-controlled studies in 664 children/adolescents aged 6-17 years with ADHD. Treatment-

emergent adverse events with the highest subject incidence rates in guanfacine hydrochloride treatment group combined were fatigue (14%), headache (23.8%) and somnolence/sedation (38%) (see **Table 3**).

Short-Term Monotherapy Trial (adolescents aged 13-17 years)
This clinical trial (Study 3) was a 15-week, double-blind, placebo-controlled study conducted in adolescents aged 13-17 years with ADHD. Treatment-emergent adverse events with the highest subject incidence rates in the guanfacine hydrochloride treatment group were decreased appetite (14.6%), dizziness (15.9%), fatigue (22.3%), headache (26.8%), sedation (11.5%) and somnolence (43.9%) (see **Table 4**).

Short-Term Adjunctive Trial (children/adolescents aged 6-17 years)
This clinical trial (Study 4) was a 9-week, placebo controlled, double-blind study conducted in children and adolescents aged 6-17 years treated with psychostimulants who were identified as having a sub optimal response to psychostimulants. Guanfacine hydrochloride was evaluated as adjunct therapy to their psychostimulant treatment. Treatment-Emergent Adverse Events with the highest subject incidence rates were headache and somnolence (see **Table 5**).

Adverse Events Leading to Discontinuation of Treatment
Twelve percent (12%) of patients (6-17 years) receiving guanfacine hydrochloride discontinued from the two pediatric monotherapy clinical studies (Studies 1 and 2) due to adverse events, compared to 4% in the placebo group. The most common adverse reactions leading to discontinuation of guanfacine hydrochloride -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/decreased blood pressure, headache, dizziness.

Six percent (5.7%) of patients (13-17 years) receiving guanfacine hydrochloride discontinued from the adolescent monotherapy clinical trial (Study 3) due to adverse events, compared to 1.9% in the placebo group. The most common adverse event leading to discontinuation of guanfacine hydrochloride - treated patients was fatigue (1.3%).

Three percent (3%) of patients receiving guanfacine hydrochloride discontinued from the adjunctive clinical study (Study 4) due to adverse events, compared to 1% in the placebo group. No adverse event to guanfacine hydrochloride causing discontinuation was reported more than once.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The developmental program for guanfacine hydrochloride included exposures in a total of 2411 participants in clinical trials (1718 children aged 6-12 years, 693 adolescent patients aged 13-17 years).

The information included in this section is based on data from 2 monotherapy forced-dose clinical trials in children and adolescents aged 6-17 years (Studies 1 and 2), 1 dose-optimized monotherapy trial in adolescents aged 13-17 years (Study 3) and 1 dose-optimized adjunctive trial in children and adolescents aged 6-17 years (Study 4).

The stated frequencies of the listed treatment-emergent adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the kind listed.

Short-Term Monotherapy Trials (children/adolescents aged 6-17 years - Studies 1 and 2)

Table 3 - Treatment-Emergent Adverse Events Reported by 1% or More and Greater Than Placebo in Pediatric Patients (aged 6-17 years) Taking guanfacine hydrochloride Alone up to 4 mg in One 8-Week or One 9-Week Controlled Clinical Trial (Studies 1 and 2)

System Organ Classes	Preferred Term	Guanfacine hydrochloride n=513 (%)	Placebo n=149 (%)
Gastrointestinal Disorders	Abdominal pain upper	9.9	7.4
	Nausea	5.7	2.0
	Dry mouth	4.1	1.3
	Constipation	2.7	0.7
	Dyspepsia	1.2	0.7
General Disorders and Administration Site Conditions	Fatigue	14.0	3.4
Investigations	Blood pressure decreased	1.9	0
	Weight increased	1.4	0
Metabolism and Nutrition Disorders	Decreased appetite	6.0	4.0
Nervous System Disorders	Somnolence	29.2	6.7
	Headache	23.8	19.5
	Sedation	9.9	4.7
	Dizziness	6.4	4.0
	Lethargy	5.7	2.7
Psychiatric Disorders	Irritability	5.8	4.0
	Nightmare	1.6	0
	Affect lability	1.4	0.7
Renal and Urinary Disorders	Enuresis	1.4	0.7
Vascular Disorders	Hypotension	2.5	0.7
	Orthostatic hypotension	1.0	0

Other common treatment-emergent adverse events (1% to 5%) included Diarrhea, Vomiting, and Insomnia.

Treatment-Emergent Adverse Events (reported by ≥1% of pediatric patients taking guanfacine hydrochloride) in other Phase 2/3 clinical trials:

Cardiac Disorders: Bradycardia
Gastrointestinal Disorders: Abdominal pain, stomach discomfort
Investigations: Blood pressure increased
Nervous System Disorders: Syncope/syncope vasovagal/loss of consciousness
Psychiatric Disorders: Anxiety, depression, middle insomnia
Respiratory, Thoracic, and Mediastinal Disorders: Asthma.

Two long-term extension studies of the above-mentioned clinical studies were conducted up to 24 months. Guanfacine hydrochloride was generally safe and well tolerated.

Short-Term Monotherapy Trial (adolescents aged 13-17 years – Study 3)

Table 4 – Treatment-Emergent Adverse Events Reported by 1% or More and Greater Than Placebo in Adolescent Patients (aged 13-17 years) Taking guanfacine hydrochloride Alone up to 7 mg in One 15-Week Controlled Clinical Trial (Study 3)

System Organ Classes	Preferred Term	Guanfacine hydrochloride n=157 (%)	Placebo n=155 (%)
Cardiac Disorders	Bradycardia	4.5	0
Gastrointestinal Disorders	Dry mouth	7.6	0
	Abdominal pain upper	6.4	4.5
	Abdominal pain	5.7	3.9
	Constipation	3.2	0
	Abdominal discomfort	1.9	1.3
General Disorders and Administration Site Conditions	Fatigue	22.3	12.3
	Asthenia	1.3	0
Investigations	Blood pressure diastolic decreased	3.2	0
	Weight increased	2.5	1.9
	Blood pressure decreased	1.9	0
Metabolism and Nutrition Disorders	Decreased appetite	14.6	13.5
Nervous System Disorders	Somnolence	43.9	21.3
	Headache	26.8	18.1
	Dizziness	15.9	10.3
	Sedation	11.5	1.9
	Insomnia	8.9	3.9
	Dizziness postural	5.1	1.9
	Initial insomnia	2.5	1.3
	Middle insomnia	2.5	0
Psychiatric Disorders	Irritability	7.0	3.9
	Nervousness	3.2	1.3
	Anxiety	2.5	1.9
	Depressed mood	1.9	0
Renal and Urinary Disorders	Enuresis	1.3	0.6
Skin and Subcutaneous Tissue Disorders	Rash	3.2	0.6
	Pruritus	1.9	1.3
Vascular disorders	Orthostatic hypotension	3.8	1.9

Short-Term Adjunctive Trial (children/adolescents aged 6-17 years – Study 4)

Table 5 - Treatment-Emergent Adverse Events Reported by 1% or More and Greater Than Placebo in Pediatric Patients (aged 6-17 years) Taking guanfacine hydrochloride up to 4 mg as an Adjunct to a Stable Dose of Psychostimulant in a Controlled Clinical

Trial (Study 4)			
System Organ Classes	**Preferred Term**	**Guanfacine hydrochloride n=302 (%)**	**Placebo n=153 (%)**
Cardiac Disorders	Bradycardia	1.7	0
Gastrointestinal Disorders	Abdominal pain upper Nausea Diarrhea Constipation Dry mouth Abdominal pain	8.3 5.0 3.6 2.3 2.0 1.7	2.0 3.3 0.7 0 0 0.7
General Disorders and Administration Site Conditions	Fatigue	9.6	2.6
Metabolism and Nutrition Disorders	Decreased appetite	6.6	3.9
Nervous System Disorders	Headache Somnolence Dizziness Sedation Dizziness postural Lethargy	21.2 13.6 7.6 4.3 1.7 1.3	13.1 4.6 3.9 2.0 0 0
Psychiatric Disorders	Insomnia Affect lability Middle insomnia Nightmare	8.6 2.3 2.3 1.3	3.9 0.7 0 0.7
Respiratory, Thoracic and Mediastinal Disorders	Asthma	1.3	0.7
Vascular Disorders	Orthostatic hypotension	2.3	0

Other common treatment-emergent adverse events (1% to 5%) included Vomiting, Stomach discomfort, Irritability, and Enuresis.

Open-label safety study (children and adolescents aged 6-17 years)

A 9-week, open-label safety study was conducted in children and adolescents aged 6-17 years with ADHD whose symptoms were not adequately controlled with psychostimulants alone. In this study, 75 patients who were receiving a stable dose of amphetamine or methylphenidate (with sub-optimal response) were provided an adjunctive, maximum tolerated guanfacine hydrochloride dose up to 4 mg/day for 9 weeks. There was no evidence of additive or unique adverse effects with the combination of guanfacine hydrochloride and psychostimulants relative to what is observed with either medication alone. There were no serious adverse events in this study. Five of 75 subjects (7%) discontinued due to adverse events. There were no evident patterns of clinical importance with regard to hematology, clinical chemistry, urinalysis or physical examination results.

Effects on Heart Rate and QT Interval

In five double-blind, randomized, placebo-controlled clinical trials in pediatric patients aged 6 17 years, the following effects on heart rate and QTc interval were observed:

Table 6 - Effects on Heart Rate (HR) and QTc[a] Interval				
Study No.[a]	**Assessment day**	**N**	**Placebo-Adjusted Mean Change from Baseline in HR bpm (90% CI)**	**Placebo-Adjusted Mean Change from Baseline in QTc ms (90% CI)**
1[b]	Day 21	217	-11.4 (-13.9, -8.9)	4.3 (0.9, 7.7)
2[b]	Day 42	176	-4.2 (-7.3, -1.1)	5.9 (2.0, 9.9)
3[b]	Day 91	109	-6.1 (-8.1, -4.0)	4.0 (1.0, 7.0)
4[c]	Day 28	116	-11.2 (-13.8, -8.6)	5.3 (1.8, 8.7)
5[c]	Day 56	107	-10.4 (-13.6, -7.2)	4.7 (0.4, 9.1)

[a]Fridericia heart rate correction $QTcF=QT/RR^{0.33}$ for studies 1,2, and 4 and study population-based heart rate correction $QTcP=QT/RR^{0.31}$ for study 5
[b]pivotal studies
[c]other clinical studies

Effects on Blood Pressure and Heart Rate
In the monotherapy, short-term (8-9 weeks), pivotal trials (Studies 1 and 2), hypotension including orthostatic hypotension was reported as an adverse drug event for 7% of the guanfacine hydrochloride group and 3% of the placebo group. Orthostatic hypotension was reported for 1% of the guanfacine hydrochloride group and none in the placebo group. In the adolescent monotherapy trial (Study 3), hypotension including orthostatic hypotension was reported as an adverse event for 8.9% of the guanfacine hydrochloride group and 3.2% in the placebo group. Orthostatic hypotension was reported as an adverse event for 3.8% of the guanfacine hydrochloride group and 1.9% of the placebo group. In the adjunctive trial (Study 4), hypotension was reported as an adverse drug event for 0.7% of the guanfacine hydrochloride group and none of the placebo group. Orthostatic hypotension was reported in 2.3% of the guanfacine hydrochloride group and none in the placebo group.

Discontinuation of Treatment
Elevations in blood pressure (up to 10mmHg) and heart rate above original baseline following withdrawal of guanfacine hydrochloride have been reported to persist in a few individuals at approximately 30 days post-dose (see **WARNINGS AND PRECAUTIONS, Cardiovascular, Elevated Blood Pressure and Heart Rate Upon Discontinuation**).

In a 26-week long-term randomized withdrawal study in children and adolescents, increases in mean systolic and diastolic blood pressure, of approximately 3 mmHg and 1 mmHg respectively were observed upon discontinuation of guanfacine hydrochloride. Increases up to 36 mmHg above normal baseline persisted in a few individuals, which ranged between 3 and 26 weeks post-dose upon discontinuation of guanfacine hydrochloride. More than 90% of patients' blood pressure measurements remained within normal limits (i.e. less than the 95th percentile based on age, sex and stature). Mean increases in pulse of approximately 1.5 bpm were observed at approximately 2 weeks after the last dose of guanfacine hydrochloride and then decreased to baseline 4 weeks later. A few cases of hypertension were observed in this study, however, the increases in blood pressure and pulse were not considered serious or associated with adverse events. One pediatric case had a serious event of withdrawal hypertension despite downward dose titration associated with the adverse event of vomiting.

8.3 Less Common Clinical Trial Adverse Reactions

The stated frequencies of the listed treatment-emergent adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the kind listed.

Short-Term Monotherapy Trials (children/adolescents aged 6-17 years - Studies 1 and 2)

Uncommon Treatment-Emergent Adverse Events (reported by ≥0.1% and <1% of pediatric patients taking guanfacine hydrochloride) in controlled clinical trials:

Cardiac Disorders: Atrioventricular block first degree, sinus arrhythmia
General Disorders and Administration Site Conditions: Asthenia, chest pain
Immune System Disorders: Hypersensitivity
Investigations: Alanine aminotransferase increased, heart rate decreased
Nervous System Disorders: Convulsion, dizziness postural, hypersomnia
Psychiatric Disorders: Agitation
Renal and Urinary Disorders: Pollakiuria
Vascular Disorders: Hypertension, pallor.

Short-Term Monotherapy Trial (adolescents aged 13-17 years – Study 3)

Uncommon Treatment-Emergent Adverse Events (reported by ≥0.1% and <1% of adolescent patients taking guanfacine hydrochloride) in controlled clinical trials:

Cardiac Disorders: Tachycardia
Eye Disorders: Vision blurred
Gastrointestinal Disorders: Dyspepsia
Investigations: Heart rate decreased, heart rate increased
Nervous System Disorders: Lethargy, syncope/loss of consciousness, tremor
Psychiatric Disorders: Affect lability, dysphoria, nightmare, sleep disorder
Renal and Urinary Disorders: Pollakiuria
Skin and Subcutaneous Tissue Disorders: Alopecia
Vascular Disorders: Hypotension, withdrawal hypertension.

Short-Term Adjunctive Trial (children/adolescents aged 6-17 years – Study 4)

Uncommon Treatment-Emergent Adverse Events (reported by ≥0.1% and <1% of pediatric/adolescent patients taking guanfacine hydrochloride as an adjunct to psychostimulant) in a controlled clinical trial:

General Disorders and Administration Site Conditions: Asthenia
Investigations: Heart rate decreased, weight increased
Nervous System Disorders: Hypersomnia, syncope/syncope vasovagal/loss of consciousness
Psychiatric Disorders: Anxiety, depression
Renal and Urinary Disorders: Pollakiuria
Vascular Disorders: Hypotension, pallor

8.6 Post-Market Adverse Reactions

The following adverse events have been identified during post-marketing experience with 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 post-marketing study involving 21,718 patients was conducted to assess the safety of immediate-release guanfacine 1 mg/day given at bedtime for 28 days. Guanfacine was administered with or without other antihypertensive agents. Adverse events reported in the post marketing 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 post-marketing study and/or reported spontaneously, not included in the guanfacine hydrochloride clinical trial adverse reactions (see **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**), include:

Cardiac Disorders: Palpitations, tachycardia
Nervous System Disorders: Paresthesia, vertigo
Eye Disorders: Vision blurred
General and Administration Site Conditions: Edema, malaise, tremor
Musculo-Skeletal System: Arthralgia, leg cramps, leg pain, myalgia
Psychiatric Disorders: Confusion, hallucination
Reproductive System and Breast Disorders: Erectile dysfunction
Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea
Skin and Subcutaneous Tissue Disorders: Alopecia, dermatitis, exfoliative dermatitis, pruritus, rash
Special Senses: Alterations in taste
Vascular Disorders: Hypertensive encephalopathy, Raynaud's Phenomenon

Suicidal Behaviour and Ideation
There have been post-marketing reports of suicide-related events, including completed suicide, suicide attempt, and suicidal ideation in patients treated with ADHD drugs. In some of these reports, comorbid conditions may have contributed to the event (see **WARNINGS AND PRECAUTIONS, Psychiatric**, **Suicidal Behaviour and Ideation**).

9 DRUG INTERACTIONS

9.2 Overview

QT Prolonging Drugs
QTc interval increase (placebo-adjusted mean change from baseline approximately 5 msec) has been observed in patients aged 6-17 years with ADHD receiving therapeutic doses of guanfacine hydrochloride at steady-state (see **WARNINGS AND PRECAUTIONS, Cardiovascular, QTc Interval** and **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**, **Effects on Heart Rate and QT Interval**).

APO-GUANFACINE XR causes a decrease in heart rate (see **WARNINGS AND PRECAUTIONS, Cardiovascular**, and **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**, **Effects on Heart Rate and QT Interval**). Given the effect of APO-GUANFACINE XR on heart rate, the concomitant use of APO-GUANFACINE XR with QT prolonging drugs is generally not recommended.

Drugs that have been associated with QTc interval prolongation and/or torsade de pointes (a polymorphic ventricular tachyarrhythmia) that can be fatal include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although

not necessarily all class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide); Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone); Class 1C antiarrhythmics (e.g., flecainide, propafenone); antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, olanzapine, risperidone); antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants e.g., amitriptyline, imipramine, maprotiline); opioids (e.g., methadone); macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, tacrolimus); quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin); antimalarials (e.g., quinine, chloroquine); azole antifungals (e.g., ketoconazole, fluconazole, voriconazole); domperidone; 5-HT3 receptor antagonists (e.g., ondansetron); tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, lapatinib, vandetanib); arsenic trioxide; histone deacetylase inhibitors (e.g., vorinostat); beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that decrease heart rate, prolong the QTc interval, or inhibit CYP3A4/CYP3A5 as well as for older drugs for which these effects have recently been established.

9.3 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 7 - Established or Potential Drug-Drug Interactions

Proper /Common name	Source of Evidence	Effect	Clinical comment
CYP3A4 and CYP3A5 Inhibitors	CT	There was a substantial increase in the rate and extent of guanfacine exposure when administered with ketoconazole; the guanfacine exposure (AUC) increased 3-fold.	Use caution when APO-GUANFACINE XR is administered to patients taking ketoconazole and other moderate and strong CYP3A4/5 inhibitors (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**), since elevation of plasma guanfacine concentration increases the risk of adverse events such as hypotension, bradycardia, and sedation.
CYP3A4 Inducers	CT	There was a significant decrease in the rate and extent of guanfacine exposure when co-administered with rifampin,	When patients are taking APO-GUANFACINE XR concomitantly with a CYP3A4 inducer, an increase in the dose of

Table 7 - Established or Potential Drug-Drug Interactions			
Proper /Common name	**Source of Evidence**	**Effect**	**Clinical comment**
		a CYP3A4 inducer. The exposure (AUC) to guanfacine decreased by 70%.	APO-GUANFACINE XR within the recommended dose range may be considered (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).
Transporters	T	Concomitant administration of guanfacine with MATE1 substrates may result in increases in the plasma concentrations of these medicinal products. Based on *in vitro* studies, guanfacine may be an inhibitor of OCT1 at maximal portal vein concentrations. Concomitant administration of guanfacine with OCT1 substrates with a similar T_{max} (e.g. metformin) may result in increases in C_{max} of these medicinal products.	Guanfacine is an *in vitro* inhibitor of MATE1 and the clinical relevance of MATE1 inhibition cannot be excluded.
Valproic Acid	CT	Co-administration of APO-GUANFACINE XR and valproic acid can result in increased concentrations of valproic acid. The mechanism of this interaction is unknown, although both guanfacine and valproic acid are metabolized by glucuronidation, possibly resulting in competitive inhibition.	When APO-GUANFACINE XR is co- administered with valproic acid, monitor patients for potential additive central nervous system (CNS) effects, and give consideration to the monitoring of serum valproic acid concentrations. Adjustments in the dose of valproic acid and APO-GUANFACINE XR may be indicated when co-administered.

Table 7 - Established or Potential Drug-Drug Interactions			
Proper /Common name	**Source of Evidence**	**Effect**	**Clinical comment**
Heart Rate-Lowering Drugs	T	APO-GUANFACINE XR causes a decrease in heart rate (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and; **ADVERSE REACTIONS, Clinical Trial Adverse Reactions**, **Less Common Clinical Trial Adverse Reactions**, **Effects on Heart Rate and QT Interval**).	The concomitant use of APO-GUANFACINE XR with other heart rate lowering drugs, such as antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, cholinesterase inhibitors, and sphingosine-1 phosphate receptor modulators is not recommended.
Antihypertensive Drugs	T	Potential for additive pharmacodynamic effects such as hypotension and syncope (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).	Use caution when APO-GUANFACINE XR is administered concomitantly with antihypertensive drugs
CNS Depressant Drugs	T	Potential for additive pharmacodynamic effects such as sedation and somnolence (see **WARNINGS AND PRECAUTIONS, General**).	Use caution when APO-GUANFACINE XR is administered concomitantly with CNS depressant drugs (e.g., alcohol, sedatives, hypnotics, benzodiazepines, barbiturates, and antipsychotics)
Oral Methylphenidate	CT	In a drug interaction study, neither APO-GUANFACINE XR (4 mg) nor methylphenidate HCl extended release (36 mg) were found to affect the pharmacokinetics of the other drug when administered concomitantly in healthy adult volunteers. The effect of methylphenidate HCl at a dose of 54 mg when administered concomitantly with APO-GUANFACINE XR was not studied.	Please see Effect.

Table 7 - Established or Potential Drug-Drug Interactions			
Proper /Common name	**Source of Evidence**	**Effect**	**Clinical comment**
Lisdexamfeta-mine Dimesylate	CT	In a drug interaction study, administration of APO-GUANFACINE XR (4 mg) to healthy adult volunteers in combination with lisdexamfetamine dimesylate (50 mg) induced a 19% increase in guanfacine maximum plasma concentrations, whereas exposure (AUC) was increased by 7%.	These small changes are not expected to be clinically meaningful. In this study, no effect on *d*-amphetamine exposure was observed following concomitant administration of APO-GUANFACINE XR and lisdexamfetamine dimesylate. Drug interaction studies have not been conducted with higher doses of lisdexamfetamine dimesylate.
Drugs That are 5-HT_{2B} Receptor Agonists	T	Please see clinical comment.	Drugs that are potent 5-HT_{2B} receptor agonists should not be used during treatment with APO-GUANFACINE XR since the risk of fibrotic complications have not been specifically studied with APO-GUANFACINE XR (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics**).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.4 Drug-Food Interactions

APO-GUANFACINE XR should not be administered with high-fat meals due to increased exposure (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).**

Grapefruit, grapefruit juice, or products containing grapefruit extract should not be used during treatment with guanfacine hydrochloride because of the risk of CYP3A4 inhibition but has not been specifically studied.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

Patients should avoid use with alcohol (see **DRUG INTERACTIONS, Drug-Drug Interactions (CNS Depressant Drugs)** and **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

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

Guanfacine is a known antihypertensive agent. By stimulating 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.

Safety Pharmacology: 5HT$_{2B}$ Receptor Agonists and Fibrotic Complications

Guanfacine demonstrates a moderate *in vitro* affinity for the 5-HT$_{2B}$ receptor, an identified likely molecular target for drug-induced valvular heart disease. Regurgitant cardiac valvular disease, primarily affecting the mitral and/or aortic valves, and other fibrotic complications have been reported in patients who took serotonergic drugs with 5-HT$_{2B}$ receptor agonist activity. The etiology of the regurgitant valvular disease is thought to be activation of 5-HT$_{2B}$ receptors on cardiac interstitial cells.

While a very small number of possible fibrotic complications, including pleural or pericardial effusion, and cardiac valvulopathy in adult patients treated with immediate release guanfacine (a compound which has been available in the USA for more than 24 years with an exposure of over 3 million person years) for hypertension have been reported, the evidence is not sufficient to establish a causal relationship between guanfacine and these fibrotic complications but a contribution of guanfacine cannot be completely ruled out in rare cases. Guanfacine has not been studied in combination with drugs that are potent 5-HT$_{2B}$ receptor agonists.

Cardiovascular Safety: Effects on Heart Rate and QT Interval

The effect of two dose levels of immediate-release guanfacine (4 mg/day and 8 mg/day) on the QT interval was evaluated in a double-blind, randomized, placebo- and active-controlled (moxifloxacin 400 mg) cross-over thorough QT study in 83 healthy adults. On Days 1 (4 mg/day) and 6 (8 mg/day), 12-lead ECGs were obtained by a continuous digital 12-lead ECG recording starting 30 minutes prior to dose administration. The ECGs were extracted within 30 to minutes of dose administration and within 10 minutes before each of the 1, 2, 3, 4, 5, 6, 8, 12, and 24-hour timepoints after dose administration. A dose-dependent decrease in heart rate was observed. The maximal placebo-adjusted mean change in heart rate was -13bpm at 8h post

dosing on day 1 in subjects receiving 4 mg/day and -22 bpm at 8h post-dosing on day 6 at the supratherapeutic dose of 8 mg/day. The maximal placebo-adjusted mean change in the QTcF interval was 5 msec at 12h post-dosing on day 1 in subjects receiving 4mg/day and 8msec at 12h post-dosing on day 6 at the supratherapeutic dose of 8 mg/day. The 12h post- dose time point at which maximal QTcF effects are seen occurs 7 hours or more after peak plasma guanfacine concentrations. Guanfacine has not been demonstrated to inhibit hERG potassium channels (see **WARNINGS AND PRECAUTIONS, Cardiovascular**, **Hypotension, Bradycardia and Syncope**; **QTc Interval**, **and ADVERSE REACTIONS, Clinical Trial Adverse Reactions**).

10.3 Pharmacokinetics

Absorption:
Guanfacine is readily absorbed after administration with guanfacine hydrochloride, with peak plasma concentrations reached approximately 5 hours after oral administration in pediatric patients (children and adolescents). In adults, the mean exposure of guanfacine increased (C_{max} ~75% and AUC ~40%) when guanfacine hydrochloride extended-release tablet was taken together with a high-fat meal, compared to intake in the fasted state.

Immediate-release guanfacine and guanfacine extended-release tablet have different pharmacokinetic characteristics, so dose substitution on a milligram for milligram basis is not appropriate because of differing pharmacokinetic profiles. Guanfacine hydrochloride extended-release tablethas a delayed T_{max}, reduced C_{max} and lower bioavailability compared to those of the same dose of immediate-release guanfacine.

Distribution:
Guanfacine is moderately bound to plasma proteins (approximately 70%), independent of drug concentration.

Metabolism:
Following absorption, the drug is rapidly and extensively metabolised by epoxidation and hydroxylation of the aromatic moiety, followed by conjugation with glucuronic acid, sulphate and glutathione.

Guanfacine is metabolized via oxidation and glucuronidation. Guanfacine is primarily metabolized by the CYP3A4 isoenzyme in human liver microsomes, and has been studied in a clinical study. In human hepatic microsomes, guanfacine did not inhibit the activities of the major cytochrome P450 isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 or CYP3A5) and is therefore unlikely to affect the clearance of other co-administered drugs metabolised by cytochrome P450s clinically; guanfacine is also not expected to be an inducer of CYP3A, CYP1A2 and CYP2B6. Guanfacine is a substrate of CYP3A4/5 and exposure is affected by CYP3A4/5 inducers and inhibitors (see **DRUG INTERACTIONS, Drug-Drug Interactions (CYP3A4 and CYP3A5 Inhibitors**; **CYP3A4 Inducers**)).

Transporters
Based on *in vitro* studies, guanfacine is a substrate of OCT1 and OCT2, but not BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1 OR MATE2. Guanfacine is not an inhibitor of BSEP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2 or MATE2K, but it is an inhibitor of MATE1 and may be an inhibitor of OCT1 at maximal portal vein concentrations.

Elimination:

Guanfacine is cleared by the kidney and the liver. The main excretion route for guanfacine is the liver. The elimination half-life of guanfacine is approximately 18 hours.

Special Populations and Conditions

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

Hepatic Insufficiency:
The impact of hepatic impairment on the pharmacokinetics of guanfacine in children and adolescents, 6-17 years old, was not assessed. Approximately 50% of the clearance of guanfacine in adults is hepatic (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Renal Insufficiency:
The impact of renal impairment on the pharmacokinetics of guanfacine in children and adolescents, 6-17 years old, was not assessed. In patients on hemodialysis, the dialysis clearance was about 15% of the total clearance (see **WARNINGS AND PRECAUTIONS, Renal**).

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15°C - 30°C.

Any unused medicinal product should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

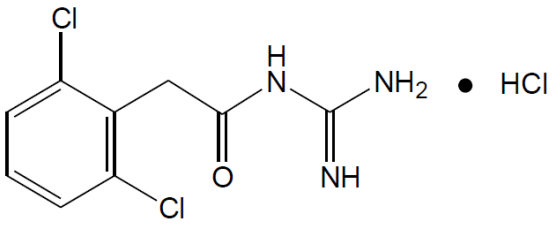
Drug Substance

Proper name: guanfacine hydrochloride

Chemical name: N-amidino-2-(2,6-dichlorophenyl) acetamide monohydrochloride

Molecular formula and molecular mass: $C_9H_9Cl_2N_3O \cdot HCl$ 282.56 g/mol

Structural formula:



Physicochemical properties: Guanfacine hydrochloride is a white or almost white powder, Sparingly soluble in water. It has relatively high solubility in methanol, sparingly soluble in alcohol and slightly soluble in acetone.

14 CLINICAL TRIALS

14.1Trial Design and Study Demographics

Table 8 - Summary of patient demographics for clinical trials in ADHD					
Study No.	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n=number)**	**Mean age (Range)**	**Sex**
Study 1	Randomized, double-blind, placebo-controlled, parallel-group, forced-dose titration study conducted in children and adolescents aged 6-17 years with ADHD	Oral, 2, 3 and 4 mg, once daily, 8 weeks	345 (6-12 yrs: 265) (13-17 yrs: 80)	10.5 yrs (6-17)	257M: 88F
Study 2[a]	Randomized, double-blind, placebo-controlled, forced-dose study conducted in children and adolescents aged 6-17 years with ADHD	Oral, 1, 2, 3 and 4 mg, once daily, 9 weeks	322 (6-12 yrs: 241) (13-17 yrs: 81)	10.5 yrs (6-17)	233M: 89F
Study 3	Randomized, double-blind, placebo-controlled, dose-optimization study conducted in adolescents aged 13-17 years with ADHD to confirm the efficacy, safety, and tolerability	Oral, 1, 2, 3, 4, 5, 6, 7 mg, once daily, 15 weeks	312	14.5 yrs (13-17)	202M: 110F
Study 4	Randomized, double-blind, placebo-controlled, dose-optimization adjunctive study with psychostimulants in children and adolescents aged 6-17 years with ADHD	Oral, 1, 2, 3 and 4 mg, once daily as an adjunct to a current, stable dose of psychostimulant, 9 weeks	455 (6-12 yrs: 361) (13-17 yrs: 94)	10.8 yrs (6-17)	326M: 129F

[a]Only patients weighing <110lbs could be randomized to 1 mg.

The efficacy of guanfacine extended-release tablet in the treatment of ADHD was established in 2 placebo-controlled monotherapy trials (Studies 1 and 2) in pediatric patients (children and adolescents; aged 6-17 years, inclusive) and in 1 placebo-controlled monotherapy trial in adolescents (aged 13-17 years). Signs and symptoms of ADHD were evaluated as the change from baseline to endpoint in ADHD Rating Scale IV (ADHD-RS-IV) scores. Daily doses used in these studies were within the range of 1- 4 mg for children and 1-7 mg in adolescents.

In Study 4, the safety and efficacy of guanfacine extended-release tablet was evaluated as adjunctive therapy in patients treated with psychostimulants (longer-acting formulations of mixed

salts of a single-entity amphetamine product, lisdexamfetamine dimesylate, methylphenidate hydrochloride extended-release, methylphenidate hydrochloride, and dexmethylphenidate hydrochloride). The study was conducted in children and adolescents aged 6-17 years with a diagnosis of ADHD, with a sub-optimal response to psychostimulants. Patients continued to take their psychostimulant in the morning and were dosed either in the morning or the evening with guanfacine extended-release tablet or with placebo in addition to their psychostimulant. Symptoms of ADHD were evaluated as the change from baseline to endpoint in ADHD Rating Scale (ADHD-RS-IV) scores. Using the Conners' Global Index-Parent (CGI-P) scale, parents made separate weekly assessments of their child's ADHD symptoms exhibited in the morning (before school) and evening (before bedtime).

14.2 Study Results

Short-Term Monotherapy Trials

Table 9 - Results of Studies 1, 2 and 3 in ADHD (Children and Adolescents aged 6-17 years)

Study No.	Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo
Study 1[a]	ADHD Rating Scale (ADHD-RS-IV) total score change from baseline to endpoint for the ITT population	Mean (SD) 2 mg: -15.40 (12.82) 3 mg: -15.79 (13.00) 4 mg: -18.96 (13.71) Comparison (placebo-adjusted difference)[b] LS mean (95% CI) -7.42 (-12.07, -2.77) p=0.0006 -7.52 (-12.19, -2.85) p=0.0005 -9.99 (-14.67, -5.32) p<0.0001	Mean (SD) -8.86 (12.90)
Study 2[c]	ADHD Rating Scale (ADHD-RS-IV) total score change from baseline to endpoint for the ITT population	Mean (SD) 1 mg: -20.4 (14.00) 2 mg: -18.0 (14.88) 3 mg: -19.4 (14.62) 4 mg: -20.9 (11.89) Comparison (placebo-adjusted difference)[b] LS mean (95% CI) -6.75 (-11.3, -2.2) p=0.0041 -5.41 (-9.9, -0.9) p=0.0176 -7.31 (-11.8, -2.8) p=0.0016 -7.88 (-12.3, -3.4) p=0.0006	Mean (SD) -12.2 (12.96)
Study 3	ADHD Rating Scale (ADHD-RS-IV) total score change from baseline to endpoint for the FAS population	Mean (SD) -25.7 (10.09) Comparison (placebo-adjusted difference) LS mean (95% CI) -6.026 (-8.865, -3.187) p<0.001	Mean (SD) -19.5 (12.63)

ITT: Intent to Treat
FAS: Full analysis set
[a]p-value and 95% CI from Dunnett's adjustment for multiple means comparisons
[b]Age subgroup analysis revealed statistically significant efficacy for only children aged 6 to 12 years
[c]Only patients weighing <110lbs could be randomized to 1 mg

In Study 1, the improvement in ADHD-RS-IV total scores at endpoint in all randomized guanfacine extended-release tablet treatment groups was statistically significantly greater than in placebo treatment groups ($p<0.001$) for each of the 2 mg, 3 mg, and 4 mg guanfacine extended-release tablet randomized treatment groups. Improvements in ADHD-RS-IV scores were observed in patients taking guanfacine extended-release tablet beginning 2 to 3 weeks after initiation of dosing.

When data were examined by age subgroups, only children aged 6 to 12 years demonstrated clinically relevant improvements.

The improvement in the ADHD-RS-IV total score demonstrated in the primary efficacy analysis was supported by the results for the ADHD-RS-IV Hyperactivity/Impulsivity and Inattentiveness subscales, Clinical Global Impression of Improvement (CGI-I), Conners' Parent Rating Scale Revised Short Form (CPRS-R:S) and Conners' Teachers Rating Scale results.

In Study 2, there were statistically significant improvements in ADHD-RS-IV total scores at endpoint in all randomized guanfacine extended-release tablet treatment groups compared to the placebo treatment groups ($p<0.02$) for each of the 2 mg, 3 mg, and 4 mg guanfacine extended-release tablet randomized treatment groups, and for the 1 mg INTUNIV XR treatment group (for patients 55-110lbs
[24.95 - 49.89kg]).

When data were examined by age subgroups, only children aged 6 to 12 years demonstrated clinically relevant improvements.

The improvement in the ADHD-RS-IV total score demonstrated in the primary efficacy analysis was supported by the results for the ADHD-RS-IV Hyperactivity/Impulsivity and Inattentiveness subscales, Clinical Global Impression of Improvement (CGI-I), and Conners' Parent Rating Scale Revised Short Form (CPRS-R:S) results.

In Study 3, subjects receiving guanfacine extended-release tablet had a statistically significant greater improvement from baseline in ADHD-RS-IV total score compared with subjects who received placebo ($p<0.001$).

The improvement in the ADHD-RS-IV total score demonstrated in the primary efficacy analysis was supported by the results of the Clinical Global Impression of Severity (CGI-S), ADHD-RS-IV Hyperactivity/Impulsivity and Inattentiveness subscales and Clinical Global Impression of Improvement (CGI-I).

Controlled, long-term efficacy studies (>9 weeks) have not been conducted in children aged 6 to 12 years and (>15 weeks) in adolescents aged 13-17 years.

<u>Short-Term Adjunctive Trial</u>

Table 10 - Results of Study 4 in ADHD (Children and Adolescents aged 6-17 years)			
Primary Endpoints	**Mean Associated value and statistical significance for Drug + Psychostimulant at all dosages (SD)**	**Mean Associated value and statistical significance for Placebo (SD)**	**LS mean[a] Comparison - placebo-adjusted difference (95% CI)**
ADHD Rating Scale (ADHD-RS-IV) total score change from baseline to endpoint for FAS population	All doses AM: -20.4 (12.77) All doses PM: -21.0 (12.39) Overall: -20.7 (12.56)	-16.0 (11.77)	-4.5 (-7.5, -1.4) p=0.002[b] -5.3 (-8.3, -2.3) p<0.001[b] -4.9 (-7.2, -2.6) p<0.001[c]

FAS – Full analysis set

[a]LS mean, and p-value were based on type III sum of squares from the ANCOVA model for the change from Baseline, including treatment group and psychostimulant type as fixed effects, and baseline value as a covariate.

[b]p-value of guanfacine extended-release tablet AM and PM groups based on Dunnett's multiple comparison procedure.

[c]p-value for all guanfacine extended-release tablet was a t-test. This was a secondary efficacy analysis.

Mean reductions in ADHD-RS-IV total scores at endpoint were significantly greater for guanfacine extended-release tablet given as an adjunct to a stable dose of psychostimulant compared to placebo given with a psychostimulant for Study 4, for both morning and evening guanfacine extended-release tablet dosing (p=0.002 and p<0.001 respectively). Both treatment groups had significantly greater improvement on the Hyperactivity/Impulsivity and Inattentive subscales of the ADHD-RS-IV compared with the placebo group regardless of time of administration.

The percentage of responders, (defined as a percentage reduction from baseline in the ADHD-RS-IV Total Score of ≥25%), were 69.7% for placebo, 79.2% for guanfacine extended-release tablet taken in the morning (AM), and 83.1% for guanfacine extended-release tabletin the evening (PM) group. The results indicated a statistically significant difference from placebo in the evening (PM) guanfacine extended-release tablet dosing group but not the morning (AM) guanfacine extended-release tablet dosing group.

Conners' Global Index-Parent (CGI-P) total score results were supportive of the primary endpoint.

Controlled long-term efficacy studies (>9 weeks) for adjunctive treatment have not been conducted.

Other Clinical Trials

A 9-week, double-blind, randomized, placebo-controlled, dose-optimization study in children aged 6-12 years with ADHD and oppositional symptoms (n=217) was conducted. Oppositional symptoms were evaluated as the change from baseline to endpoint in the Oppositional

Subscale of the Conners' Parent Rating Scale – revised Long Form (CPRS-R:L) score. The mean reduction in the CPRS-R:L at endpoint was significantly greater for guanfacine extended-release tablet compared to placebo. ADHD-RS-IV Hyperactivity/Impulsivity and Inattention subscales results supported the pivotal study primary endpoint results. CGI-I and CGI-S rating scales and the 40- item Conduct Problem Scale of the New York Parent's Rating Scale (NYPRS-S) results also support the primary efficacy endpoint in treating oppositional symptoms and conduct problems in children with a diagnosis of ADHD.

A 9-week, double-blind, randomized, placebo-controlled, dose-optimization study in children aged 6-12 years to assess the efficacy of once daily dosing with optimized guanfacine extended-release tablet administered either in the morning or the evening was conducted. Symptoms of ADHD were evaluated as the change from baseline to endpoint in ADHD Rating Scale (ADHD-RS-IV) Total Score. Guanfacine extended-release tablet showed significantly ($p<0.001$) greater improvement compared to placebo on the change from baseline to endpoint in the ADHD rating scale (ADHD-RS-IV) score regardless of time of administration (morning or evening) of guanfacine extended-release tablet. Conners' Parent Rating Scale – Revised Short Form (CPRS-R:S) results were supportive of the primary endpoint. CPRS total scores, Weiss Functional Impairment Rating Scale - Parent (WFIRS-P) global score and WFIRS-P domain subscale scores for Family, Learning and School, Academic Performance, Behaviour in School, Social Score, and Risk score results were also supportive of the primary endpoint.

A 15-week, double-blind, dose-optimization, safety and tolerability study compared the effects of guanfacine extended-release tablet to placebo using the Choice Reaction Time Test from the Cambridge Neuropsychological Test Automated Battery (CANTAB) in patients aged 6 17 years (n=182).

Patients were titrated to an optimal dose within a 1-3 mg range. There was no evidence of impairment in speed processing compared to placebo. The 5-point Pictorial Sleepiness Scale (PSS), designed to assess sleepiness in school-age children and adolescents, was used to measure sleepiness throughout the course of the day and study. Patient and observer (healthcare professional) reported outcomes on the PSS were similar during the daytime in a classroom setting for the guanfacine extended-release tablet and placebo groups. However, patients and observer (parent) scores suggested a greater degree of sleepiness in the evening hours before bedtime in the guanfacine extended-release tablet group compared to the placebo group. These trends were consistent throughout the study. The frequency and intensity of sedative adverse events was similar in this study to that observed in the pivotal studies.

14.3 Comparative Bioavailability studies

A randomized, single-dose, two-way crossover comparative bioavailability study of Apo-Guanfacine XR 4 mg extended-release tablets (Apotex Inc.) and Intuniv XR® 4 mg tablets (Shire Pharma Canada ULC) was conducted under fed conditions in healthy male volunteers. The results obtained from 38 volunteers who completed the study are summarized in the following table.

Table 11 – Summary of Comparative Bioavailability Data

Guanfacine
(1 x 4 mg)
Geometric Mean
Arithmetic Mean (CV%)

Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (pg•h/mL)	149822.6 153304.1 (20.9)	152442.9 157533.5 (24.4)	98.3	93.2 - 103.7
AUC_I (pg•h/mL)	155989.1 159960.5 (21.9)	159001.8 164684.5 (25.3)	98.1	93.1 - 103.4
C_{max} (pg/mL)	5833.6 5890.2 (13.9)	6128.9 6252.4 (19.7)	95.2	90.7 - 99.9
T_{max}[3] (h)	11.00 (5.00 – 18.00)	8.50 (5.00 – 14.00)		
$T_{1/2}$[4] (h)	14.21 (15.2)	14.27 (16.3)		

[1] Apo-Guanfacine XR (guanfacine hydrochloride) extended-release tablets, 4 mg (Apotex Inc.)
[2] Intuniv XR® (guanfacine hydrochloride) extended- release tablets, 4mg (Shire Pharma Canada ULC).
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

A randomized, single-dose, two-way crossover comparative bioavailability study of Apo-Guanfacine XR 4 mg extended-release tablets (Apotex Inc.) and Intuniv XR® 4 mg tablets (Shire Pharma Canada ULC) was conducted under fasting conditions in healthy male volunteers. The results obtained from 96 volunteers who completed the study are summarized in the following table.

Table 12 – Summary of Comparative Bioavailability Data

Guanfacine (1 x 4 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_t (pg•h/mL)	101917.6 106536.2 (28.4)	95155.4 100616.8 (33.4)	107.1	100.4 - 114.3
AUC_I (pg•h/mL)	107908.2 113501.5 (30.7)	99907.0 106084.1 (34.7)	108.0	101.2 - 115.3
C_{max} (pg/mL)	3262.3 3426.4 (32.3)	3448.7 3660.0 (36.6)	94.6	87.3 - 102.5
T_{max}[3] (h)	6.50 (3.50 – 36.10)	4.50 (3.00 – 24.08)		
$T_{1/2}$[4] (h)	14.65 (24.0)	14.41 (16.3)		

[1] Apo-Guanfacine XR (guanfacine hydrochloride) extended-release tablets, 4mg (Apotex Inc.)
[2] Intuniv XR® (guanfacine hydrochloride) extended release tablets, 4 mg (Shire Pharma Canada ULC).
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (CV%) only

16 NON-CLINICAL TOXICOLOGY

No carcinogenic effect of guanfacine was observed in studies of 78 weeks in mice or 102 weeks in rats at doses up to 6.8 times the maximum recommended human dose of 0.12 mg/kg/day on a mg/m^2 basis.

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.

No adverse effects were observed in fertility studies in male and female rats at doses up to 22 times the maximum recommended human dose on a mg/m^2 basis.

Rat experiments have shown that guanfacine crosses the placenta. However, administration of guanfacine to rats and rabbits at 4 and 2.7 times, respectively, the maximum recommended human dose of 0.12 mg/kg/day on a mg/m^2 basis resulted in no evidence of harm to the fetus. Higher doses (13.5 times the maximum recommended human dose in both rabbits and rats) were associated with reduced fetal survival and maternal toxicity.

17 SUPPORTING PRODUCT MONOGRAPHS

1 INTUNIV XR® Tablets, 1 mg, 2 mg, 3 mg and 4 mg, submission control no. 240952, Product Monograph, Takeda Canada Inc. DEC 03, 2020.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-GUANFACINE XR
Guanfacine Extended-Release Tablets

Read this carefully before you start taking **APO-GUANFACINE XR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-GUANFACINE XR**.

What is APO-GUANFACINE XR used for?

- APO-GUANFACINE XR is used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents 6-17 years of age. It can be used alone or with another medicine called a psychostimulant.
  APO-GUANFACINE XR may be a part of your/your child's overall treatment plan for ADHD. The doctor may also recommend counselling or other therapy.

How does APO-GUANFACINE XR work?
APO-GUANFACINE XR contains guanfacine. Guanfacine is not a central nervous system (CNS) stimulant. The exact way guanfacine works to treat ADHD in not known. APO-GUANFACINE XR is thought to affect receptors (alpha$_{2A}$-adrenergic receptors) in the brain to reduce nerve impulses. This helps increase attention (including the ability to follow and finish tasks) and decrease impulsiveness and hyperactivity in patients with ADHD.

What are the ingredients in APO-GUANFACINE XR?
Medicinal ingredient: guanfacine (as guanfacine hydrochloride)
Non-medicinal ingredients: Anhydrous Lactose, colloidal silicon dioxide, fumaric acid, hypromellose, indigotine aluminium lake, magnesium stearate, and yellow ferric oxide

APO-GUANFACINE XR comes in the following dosage forms:
Extended-Release Tablets; 1 mg, 2 mg, 3 mg, and 4 mg

Do not use APO-GUANFACINE XR if:

- You/your child are/is allergic to guanfacine or any other non-medicinal ingredients in APO-GUANFACINE XR. (see What are the ingredients in APO-GUANFACINE XR?)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-GUANFACINE XR. Talk about any health conditions or problems you may have, including if you or your child:

- has a heart problem such as:
  - a very slow heart rate (pulse)
  - a heart rhythm problem (arrhythmia)
  - heart disease
  - congestive heart failure
  - a hereditary disorder of the heart's electrical system (called congenital long QT syndrome)

- has fainted in the past (or has a history of fainting)

- has low or high blood pressure
- has liver or kidney problems
- have mental health problems or a family history of mental health problems including psychosis, mania, bipolar illness, depression, or suicide
- has any other medical condition
- is pregnant. Your doctor will decide if you can take this medicine if you are pregnant.
- is breast-feeding or plans to breast-feed. It is not known if APO-GUANFACINE XR passes into breast milk.

Other warnings you should know about:

The following have been reported with use of medicines used to treat ADHD such as APO-GUANFACINE XR:

Mental Health problems (psychiatric):

Suicidal behaviour and thoughts: **New or worsening** thoughts or feelings related to:
- thoughts about suicide (thinking about or feeling like killing yourself)
- suicide actions (a suicide attempt or completed suicide)

Suicidal thoughts or behaviours may occur at any time during treatment, particularly:
- when you or your child starts treatment
- when there is a change to the dose
- after you or your child stops taking APO-GUANFACINE XR

Should this happen to you or your child, talk to the doctor right away.

Bipolar Disorder: **New or worsening** bipolar illness (extreme mood swings with periods of mania (unusually excited, over-active or un-inhibited) alternating with periods of depression (feelings of sadness, worthlessness or hopelessness). Tell your doctor/child's doctor about:
- any mental health problems you or your child has
- family history of suicide, bipolar disorder or depression

Psychotic or Manic Symptoms: **New or worsening** of psychotic or manic symptoms can occur when taking APO-GUANFACINE XR at usual doses. Symptoms can include:
- hallucinations (hearing voices, believing things that are not true or feeling suspicious)
- feeling unusually excited, over-active or un-inhibited

Call the doctor right away if you or your child has any new or worsening mental health symptoms while taking APO-GUANFACINE XR, especially seeing or hearing things that are not real, believing things that are not real, or you start feeling suspicious.

Aggressive behaviour: **New or worse** aggressive behaviour, hostility can occur.

These new or worsening mental health problems may be more likely to occur if your child has mental disorders that you may or may not have known about.

Feeling sleepy/drowsy: APO-GUANFACINE XR can make you or your child feel sleepy and drowsy. Avoid doing tasks that require special attention such as riding a bike, driving/operating machinery or doing other dangerous activities until you know how APO-GUANFACINE XR affects you or your child. If you notice you or your child is feeling sleepy or drowsy often, talk to the doctor.

Do NOT take APO-GUANFACINE XR with alcohol or other medicines that make you or your child feel sleepy or drowsy. This can make it worse.

Dehydration: While on APO-GUANFACINE XR, you/your child should avoid becoming dehydrated or overheated.

Weight: Talk to your doctor or your child's doctor or pharmacist about any problem with weight while taking APO-GUANFACINE XR.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-GUANFACINE XR:
- Ketoconazole (used to treat yeast or fungal infections)
- Rifampin (used to treat tuberculosis (TB))
- Valproic acid (used to treat bipolar disorder)
- Drugs that can lower your heart rate, such as antiarrhythmics and beta blockers
- Drugs used to treat chest pain (angina)
- Drugs used to treat high blood pressure
- Drugs that can cause QT prolongation
- Drugs that can increase your risk of fainting
- Drugs that cause sleepiness (sedatives)
- Drugs inducing sleep in surgical anesthesia or in the treatment of insomnia (hypnotics)
- Drugs used as tranquilizer (benzodiazepines)
- Drugs used as central nervous system depressants (barbiturates)
- Drugs used to treat psychosis (antipsychotics)
- Alcohol
- Other drugs for ADHD (such as methylphenidate, lisdexamfetamine dimesylate)
- Any drug that may cause heart valve problems
- Grapefruit, grapefruit juice or products containing grapefruit extract

How to take APO-GUANFACINE XR:

Monitoring: your doctor or your child's doctor should monitor your/your child's heart rate and blood pressure before starting treatment, periodically during treatment, when the dose is changed and after stopping treatment.

Take/give APO-GUANFACINE XR:
- exactly as your doctor or your child's doctor has told you.
- once a day, either alone or with an ADHD psychostimulant medication prescribed by your doctor or your child's doctor. The doctor will tell you when you/your child should take APO-GUANFACINE XR and when to take the other ADHD psychostimulant medication.
- **Swallow the tablet whole with a small amount of liquid. Do NOT crush, chew or break the tablet before swallowing and Do NOT take it with a high-fat meal.**

Stopping APO-GUANFACINE XR:
Do NOT stop taking APO-GUANFACINE XR or giving it to your child without talking to the doctor first. Stopping this medication suddenly may lead to a serious increase in blood pressure and heart rate. **The doctor will decrease the dose slowly over time to avoid side effects.** This is especially important if you/your child are taking a psychostimulant along with

APO-GUANFACINE XR.

Usual child and adolescent (6-17 years of age) dose: The recommended starting dose is 1 mg tablet once a day. The doctor may change the dose until it is right for you/your child.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-GUANFACINE XR, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Possible symptoms of an overdose include:

- low blood pressure
- initial high blood pressure
- slowing of heart rhythm
- trouble breathing
- feeling tired/having low energy

Missed Dose:

- If you miss two or more doses in a row, talk to your doctor or your child's doctor. The doctor may need to restart you/your child on a lower dose.

What are possible side effects from using APO-GUANFACINE XR?

These are not all the possible side effects you may feel when taking APO-GUANFACINE XR. If you experience any side effects not listed here, contact your healthcare professional.

- Feeling sleepy, trouble sleeping
- Feeling tired
- Feeling dizzy
- Headache
- Nausea
- Stomach pain
- Not feeling hungry (decreased appetite)
- Feeling drowsy
- Dry mouth
- Constipation

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Low blood pressure		x	
Feeling sleepy		x	
UNCOMMON			
Low heart rate (pulse)		x	

Fainting		x	
Convulsions: seizure, spasms, shaking or fits		x	
UNKNOWN			
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			x
New Psychotic or Manic Symptoms: Paranoia, delusions		x	
Hallucinations: seeing, feeling or hearing things that are not there		x	
Mania: feeling unusually excited, over-active, or un-inhibited		x	
Aggressive Behaviour or Hostility		x	
Suicidal Behaviour: Thoughts or actions about hurting or killing yourself.			x
High Blood Pressure after suddenly stopping APO-GUANFACINE XR: headaches, feeling confused, nervousness, agitation, tremors			x

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature 15°C to 30°C.

Keep out of reach and sight of children.

If you want more information about APO-GUANFACINE XR:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Patient Medication Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

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