

PRODUCT MONOGRAPH

Pr **INTUNIV XR**^{®*}

guanfacine hydrochloride extended-release tablets

1mg, 2mg, 3mg, 4mg
guanfacine (as guanfacine HCl)

selective α_{2A} -adrenergic receptor agonist

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PrINTUNIV XR®

guanfacine hydrochloride extended-release tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	Tablet / 1mg, 2mg, 3mg, 4mg guanfacine as guanfacine HCl	Crospovidone, fumaric acid, glyceryl behenate, green pigment blend PB-1763 (3mg and 4mg tablets only), hypromellose, lactose, methacrylic acid copolymer, microcrystalline cellulose, and povidone.

INDICATIONS AND CLINICAL USE

Pediatrics (6 -17 years of age)

INTUNIV XR (guanfacine hydrochloride 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.

INTUNIV 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

INTUNIV 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 INTUNIV 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 INTUNIV XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Pediatrics (<6 years of age)

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

Adults (≥18 years of age)

INTUNIV XR has not been systematically studied in and is therefore not indicated for use in adults (over 18 years of age).

CONTRAINDICATIONS

Hypersensitivity

Patients with a history of hypersensitivity to this drug, to any ingredient in the formulation or component of the container, or to any other product containing guanfacine (see **Dosage Forms, Composition and Packaging**).

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 trials (Studies 1 and 2) in 6-17 year olds, sedative events reported as adverse reactions were 38% for INTUNIV XR vs. 12% for placebo and in a separate monotherapy trial in adolescents (Study 3), were 54% for INTUNIV XR vs. 23% for placebo. In an adjunctive trial (Study 4) in 6-17 year olds, sedative events reported as adverse events were 18% for INTUNIV XR vs. 7% for placebo. INTUNIV XR 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 INTUNIV 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 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 INTUNIV XR does not adversely affect them. Patients should avoid use with alcohol (see **Drug Interactions, Drug-Drug Interactions - CNS Depressant Drugs; Dosage and Administration, Dosing Considerations**).

Cardiovascular

Hypotension, Bradycardia and Syncope

INTUNIV XR can cause syncope and dose-dependent decreases in heart rate and blood pressure (systolic and diastolic) (see **Adverse Reactions, Clinical Trial Adverse Drug Reactions – Effects on Blood Pressure and Heart Rate; Action and Clinical Pharmacology, Cardiovascular Safety**). 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 5mmHg, 3mmHg, and 6bpm, respectively, for all dose groups combined (generally one week after reaching target doses of 1mg/day, 2mg/day, 3mg/day or 4mg/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 5mmHg, 4mmHg, and 6bpm 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 4mmHg, 3mmHg, and 9bpm, 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 INTUNIV 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 INTUNIV XR can decrease blood pressure and heart rate. Caution is advised when treating patients with INTUNIV 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 INTUNIV 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 - QT Prolonging Drugs; Adverse Reactions, Clinical Trial Adverse Drug 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 INTUNIV 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 INTUNIV XR.

To minimize the risk of an increase in blood pressure upon discontinuation, the total daily dose of INTUNIV XR should be tapered in decrements of no more than 1mg every 3 to 7 days. Patients should be monitored during dose downward titration and following INTUNIV XR discontinuation until blood pressure and heart rate have returned to baseline (see **Monitoring and Laboratory Tests; Dosage and Administration, 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 10mmHg 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 3mmHg and 1mmHg respectively were observed upon discontinuation of INTUNIV XR. Increases up to 36mmHg above normal baseline persisted in a few individuals, which ranged between 3 and 26 weeks post-dose upon discontinuation of INTUNIV XR. 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 1.5bpm were observed at approximately 2 weeks after the last dose of INTUNIV XR 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 Drug Reactions – Effects on Blood Pressure and Heart Rate; 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 INTUNIV XR treatments in patients on adjunctive therapy. Caution is warranted if a patient stops INTUNIV XR while maintaining its psychostimulant therapy. Use caution when prescribing drugs that can elevate blood pressure and heart rate immediately following INTUNIV XR discontinuation (see **Drug Interactions, Drug-Drug Interactions**).

QTc Interval

QTc increase (placebo-adjusted mean change from baseline approximately 5msec) has been observed in patients aged 6-17 years with ADHD receiving therapeutic doses of INTUNIV XR at steady-state. In clinical trials of INTUNIV XR in ADHD patients, there were no reports of torsade de pointes. Given the effect of INTUNIV XR on cardiac electrophysiology, consider this observation in clinical decisions to prescribe INTUNIV XR 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 Drug Reactions - Effects on Heart Rate and QT Interval; Drug Interactions, Drug-Drug Interactions - QT Prolonging Drugs**).

Psychiatric

Pre-existing Psychosis

Administration of medications for ADHD may exacerbate symptoms of behavior 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 INTUNIV 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 behavior 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 behavior or hostility, patients beginning treatment of ADHD should be monitored for the appearance of, or worsening of, aggressive behavior or hostility.

Suicidal Behavior 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 behavior. Therefore, it is recommended for patients treated with ADHD drugs that caregivers and physicians monitor for signs of suicide-related behavior, 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 behavior 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.

Dependence Liability

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

Effects on Growth

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

Special Populations

Pregnant Women

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

Nursing Women

There are no clinical data on the use of INTUNIV XR 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 INTUNIV XR is administered to a woman who is breast feeding.

Pediatrics (<6 years of age)

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

Adults (≥18 years of age)

The safety and efficacy of INTUNIV XR in adults (≥18 years) have not been studied.

Use in Renally Impaired Patients

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, Dosage Adjustment for Special Populations**).

Use in Hepatically Impaired Patients

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, Dosage Adjustment for Special Populations**).

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 INTUNIV XR (see **Warnings and Precautions, Cardiovascular; Dosage and Administration, Dosing Considerations; 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The developmental program for INTUNIV XR 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).

Adverse Events Leading to Discontinuation of Treatment

Twelve percent (12%) of patients (6-17 years) receiving INTUNIV XR 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 INTUNIV XR-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 INTUNIV XR 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 INTUNIV XR-treated patients was fatigue (1.3%).

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

Clinical Trial Adverse Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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)

The two forced-dose clinical trials (Studies 1 and 2) with INTUNIV XR 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 INTUNIV XR treatment group combined were fatigue (14%), headache (23.8%) and somnolence/sedation (38%).

Table 1: Treatment-Emergent Adverse Events Reported by 1% or More and Greater Than Placebo in Pediatric Patients (aged 6-17 years) Taking INTUNIV XR Alone up to 4mg in One 8-Week or One 9-Week Controlled Clinical Trial (Studies 1 and 2)			
System Organ Classes	Preferred Term	INTUNIV XR 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.

Uncommon Treatment-Emergent Adverse Events (reported by $\geq 0.1\%$ and $< 1\%$ of pediatric patients taking INTUNIV XR) 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.

Treatment-Emergent Adverse Events (reported by $\geq 1\%$ of pediatric patients taking INTUNIV XR) 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. INTUNIV XR was generally safe and well tolerated.

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 INTUNIV XR treatment group were decreased appetite (14.6%), dizziness (15.9%), fatigue (22.3%), headache (26.8%), sedation (11.5%) and somnolence (43.9%).

System Organ Classes	Preferred Term	INTUNIV XR n=157 (%)	Placebo n=155 (%)
Cardiovascular 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

Table 2: Treatment-Emergent Adverse Events Reported by 1% or More and Greater Than Placebo in Adolescent Patients (aged 13-17 years) Taking INTUNIV XR Alone up to 7mg in One 15-Week Controlled Clinical Trial (Study 3)			
System Organ Classes	Preferred Term	INTUNIV XR n=157 (%)	Placebo n=155 (%)
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

Uncommon Treatment-Emergent Adverse Events (reported by $\geq 0.1\%$ and $< 1\%$ of adolescent patients taking INTUNIV XR) 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)

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. INTUNIV XR was evaluated as adjunct therapy to their psychostimulant treatment. Treatment-Emergent Adverse Events with the highest subject incidence rates were headache and somnolence.

Table 3: Treatment-Emergent Adverse Events Reported by 1% or More and Greater Than Placebo in Pediatric Patients (aged 6-17 years) Taking INTUNIV XR up to 4mg as an Adjunct to a Stable Dose of Psychostimulant in a Controlled Clinical Trial (Study 4)			
System Organ Classes	Preferred Term	INTUNIV XR n=302 (%)	Placebo n=153 (%)
Cardiac Disorders	Bradycardia	1.7	0
Gastrointestinal Disorders	Abdominal pain upper	8.3	2.0
	Nausea	5.0	3.3
	Diarrhea	3.6	0.7
	Constipation	2.3	0
	Dry mouth	2.0	0
	Abdominal pain	1.7	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	21.2	13.1
	Somnolence	13.6	4.6
	Dizziness	7.6	3.9
	Sedation	4.3	2.0
	Dizziness postural	1.7	0
	Lethargy	1.3	0
Psychiatric Disorders	Insomnia	8.6	3.9
	Affect lability	2.3	0.7
	Middle insomnia	2.3	0
	Nightmare	1.3	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.

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

General Disorders and Administration Site Conditions: Asthenia

Investigations Disorders: 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.

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 INTUNIV XR dose up to 4mg/day for 9 weeks. There was no evidence of additive or unique adverse effects

with the combination of INTUNIV XR 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:

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

*Fridericia heart rate correction $QTcF=QT/RR^{0.33}$ for studies 1,2, & 4 and study population-based heart rate correction $QTcP=QT/RR^{0.31}$ for study 5; **pivotal studies;***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 INTUNIV XR group and 3% of the placebo group. Orthostatic hypotension was reported for 1% of the INTUNIV XR 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 INTUNIV XR group and 3.2% in the placebo group. Orthostatic hypotension was reported as an adverse event for 3.8% of the INTUNIV XR 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 INTUNIV XR group and none of the placebo group. Orthostatic hypotension was reported in 2.3% of the INTUNIV XR 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 INTUNIV XR have been reported to persist in a few individuals at approximately 30 days post-dose (see **Warnings and Precautions, 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 3mmHg and 1mmHg respectively were observed upon discontinuation of INTUNIV XR. Increases up to 36mmHg above normal baseline persisted in a few individuals, which ranged between 3 and 26 weeks post-dose upon discontinuation of INTUNIV XR. 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 1.5bpm were observed at approximately 2 weeks after the last dose of INTUNIV XR 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.

Post-Market Adverse Drug 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 1mg/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 INTUNIV XR clinical trial adverse reactions (see **Clinical Trial Adverse Drug Reactions**), include:

Cardiovascular: Palpitations, tachycardia

Central Nervous System: Paresthesia, vertigo

Eye Disorders: Vision blurred

General and Administration Site Conditions: Edema, malaise, tremor

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

Psychiatric: Confusion, hallucination

Reproductive System, Male: Erectile dysfunction

Respiratory System: Dyspnea

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

Special Senses: Alterations in taste

Vascular Disorders: Hypertensive encephalopathy, Raynaud's Phenomenon

Suicidal Behavior 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, Suicidal Behavior and Ideation**).

DRUG INTERACTIONS

Drug-Drug Interactions

CYP3A4 and CYP3A5 Inhibitors

Use caution when INTUNIV XR is administered to patients taking ketoconazole and other moderate and strong CYP3A4/5 inhibitors (see **Dosage and Administration, Dosage Adjustment for Special Populations**), since elevation of plasma guanfacine concentration increases the risk of adverse events such as hypotension, bradycardia, and sedation. There was a substantial increase in the rate and extent of guanfacine exposure when administered with ketoconazole; the guanfacine exposure (AUC) increased 3-fold.

CYP3A4 Inducers

When patients are taking INTUNIV XR concomitantly with a CYP3A4 inducer, an increase in the dose of INTUNIV XR within the recommended dose range may be considered (see **Dosage and Administration, Dosage Adjustment for Special Populations**). There was a significant decrease in the rate and extent of guanfacine exposure when co-administered with rifampin, a CYP3A4 inducer. The exposure (AUC) to guanfacine decreased by 70%.

Valproic Acid

Co-administration of INTUNIV 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 INTUNIV 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 INTUNIV XR may be indicated when co-administered.

Heart Rate-Lowering Drugs

INTUNIV XR causes a decrease in heart rate (see **Warnings and Precautions, Cardiovascular; Adverse Reactions, Clinical Trial Adverse Drug Reactions - Effects on Heart Rate and QT Interval**). The concomitant use of INTUNIV 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.

QT Prolonging Drugs

QTc interval increase (placebo-adjusted mean change from baseline approximately 5msec) has been observed in patients aged 6-17 years with ADHD receiving therapeutic doses of INTUNIV XR at steady-state (see **Warnings and Precautions, Cardiovascular - QTc Interval; Adverse Reactions, Clinical Trial Adverse Drug Reactions - Effects on Heart Rate and QT Interval**).

INTUNIV XR causes a decrease in heart rate (see **Warnings and Precautions, Cardiovascular; Adverse Reactions, Effects on Heart Rate and QT Interval**). Given the effect of

INTUNIV XR on heart rate, the concomitant use of INTUNIV 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 IC 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.

Antihypertensive Drugs

Use caution when INTUNIV XR is administered concomitantly with antihypertensive drugs, due to the potential for additive pharmacodynamic effects such as hypotension and syncope (see **Warnings and Precautions, Cardiovascular**).

CNS Depressant Drugs

Use caution when INTUNIV XR is administered concomitantly with CNS depressant drugs (e.g., alcohol, sedatives, hypnotics, benzodiazepines, barbiturates, and antipsychotics) due to the potential for additive pharmacodynamic effects such as sedation and somnolence (see **Warnings and Precautions, General**).

Oral Methylphenidate

In a drug interaction study, neither INTUNIV XR (4mg) nor methylphenidate HCl extended-release (36mg) 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 54mg when administered concomitantly with INTUNIV XR was not studied.

Lisdexamfetamine Dimesylate

In a drug interaction study, administration of INTUNIV XR (4mg) to healthy adult volunteers in combination with lisdexamfetamine dimesylate (50mg) 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 INTUNIV 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

Drugs that are potent 5-HT_{2B} receptor agonists should not be used during treatment with INTUNIV XR since the risk of fibrotic complications have not been specifically studied with INTUNIV XR and therefore should not be used (see **Detailed Pharmacology, Pharmacodynamics**).

Drug-Food Interactions

INTUNIV 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 INTUNIV XR because of the risk of CYP3A4 inhibition but has not been specifically studied.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

INTUNIV 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 INTUNIV XR as an adjunctive therapy with psychostimulants is 1mg, taken orally once a day; evening dosing may be considered (see **Clinical Trials**).

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. INTUNIV 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 INTUNIV XR in pediatric patients less than 25kg/55lbs 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; 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; Dosage and Administration, Discontinuation**).

Recommended Dose and Dosage Adjustment in Children (6-17 years old)

The recommended starting dose for both INTUNIV XR monotherapy and adjunct therapy to psychostimulants is 1mg, 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 1mg per week up to a maximum daily dose of 4mg (6-12 years) or 7mg (13-17 years), for monotherapy and up to a maximum daily dose of 4mg 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 INTUNIV XR, is 0.05-0.12 mg/kg/day (total daily dose 1-7mg).

Recommended Target Dose Range for INTUNIV XR monotherapy* (depending on clinical response and tolerability)	
Weight	Target dose range (0.05 - 0.12 mg/kg/day)
25.0-33.9kg	2- 3 mg/day
34.0-41.4kg	2- 4 mg/day
41.5-49.4kg	3- 5 mg/day
49.5-58.4kg	3- 6 mg/day
≥58.5kg	4- 7 mg/day

***Doses above 4mg/day have not been evaluated in children (ages 6-12 years) and doses above 7mg/day have not been evaluated in adolescents (ages 13-17 years)**

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

Missed Dose

If two or more consecutive doses are missed, re-titration is recommended based on the patient's tolerability to INTUNIV XR (see **Dosage and Administration, Discontinuation**).

Discontinuation

Patients/caregivers should be instructed not to discontinue INTUNIV 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, Elevated Blood Pressure and Heart Rate Upon Discontinuation; 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 INTUNIV XR monotherapy. Patients should be monitored during dose downward titration and following INTUNIV 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 INTUNIV 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 INTUNIV XR discontinuation (see **Drug Interactions, Drug-Drug Interactions**).

Dosage Adjustment for Special Populations

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, Special Populations – Use in Renally Impaired Patients**).

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, Special Populations – Use in Hepatically Impaired Patients**).

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 7mg, may be considered if needed. If the inducing treatment is ended, retitration to reduce the guanfacine dose is recommended during the following weeks.

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 INTUNIV 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacodynamics

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

Guanfacine is a known antihypertensive agent. By stimulating α_{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.

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 INTUNIV XR 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 INTUNIV XR 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. INTUNIV XR 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 INTUNIV XR. 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, Behavior 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 INTUNIV XR 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 1-3mg 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 INTUNIV XR and placebo groups. However, patients and observer (parent) scores suggested a greater degree of sleepiness in the evening hours before bedtime in the INTUNIV XR 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.

Cardiovascular Safety

Effects on Heart Rate and QT Interval: (see **Warnings and Precautions, Cardiovascular - Hypotension, Bradycardia and Syncope; QTc Interval; Adverse Reactions, Clinical Trial Adverse Drug Reactions**).

The effect of two dose levels of immediate-release guanfacine (4mg/day and 8mg/day) on the QT interval was evaluated in a double-blind, randomized, placebo- and active-controlled (moxifloxacin 400mg) cross-over thorough QT study in 83 healthy adults. On Days 1 (4mg/day) and 6 (8mg/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 10 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 4mg/day and -22bpm at 8h post-dosing on day 6 at the suprathreshold dose of 8mg/day. The maximal placebo-adjusted mean change in the QTcF interval was 5msec at 12h post-dosing on day 1 in subjects receiving 4mg/day and 8msec at 12h post-dosing on day 6 at the suprathreshold dose of 8mg/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.

Pharmacokinetics

Absorption

Guanfacine is readily absorbed after administration with INTUNIV XR, 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 INTUNIV XR was taken together with a high-fat meal, compared to intake in the fasted state.

Immediate-release guanfacine and INTUNIV XR have different pharmacokinetic characteristics, so dose substitution on a milligram for milligram basis is not appropriate because of differing pharmacokinetic profiles. INTUNIV XR has 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

Guanfacine is metabolized via oxidation and glucuronidation. Guanfacine is primarily metabolized by the CYP3A4 isoenzyme. In human hepatic microsomes, guanfacine did not inhibit the activities of the major cytochrome P450 isoenzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 or CYP3A5). 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**).

Excretion

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 INTUNIV XR 4mg, 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 Impairment

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, Special Populations - Use in Hepatically Impaired Patients**).

Renal Impairment

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, Special Populations - Use in Renally Impaired Patients**).

STORAGE AND STABILITY

Store at 25°C (77°F); excursions permitted from 15° to 30°C (59° to 86°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

INTUNIV XR (guanfacine hydrochloride extended-release tablets) is designed as a tablet for once-a-day oral administration.

Each INTUNIV XR tablet contains guanfacine hydrochloride equivalent to 1mg, 2mg, 3mg and 4mg of guanfacine base and the following inactive ingredients: crospovidone, fumaric acid, glyceryl behenate, hypromellose, lactose, methacrylic acid copolymer, microcrystalline cellulose and povidone. In addition, the 3mg and 4mg tablets also contain green pigment blend PB-1763.

INTUNIV XR tablets 1mg: white/off-white, round (debossed on top 503/on bottom 1mg), bottles of 100.

INTUNIV XR tablets 2mg: white/off-white, oblong (debossed on top 503/on bottom 2mg), bottles of 100.

INTUNIV XR tablets 3mg: green, round (debossed on top 503/on bottom 3mg), bottles of 100.

INTUNIV XR tablets 4mg: green, oblong (debossed on top 503/on bottom 4mg), bottles of 100.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

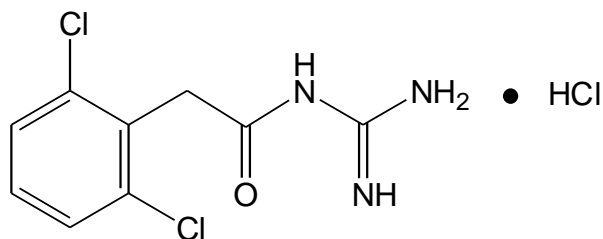
Drug Substance

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

Structural formula:



Physicochemical properties: Guanfacine hydrochloride is a white to off-white crystalline powder, sparingly soluble in water (approximately 1mg/mL). The only organic solvent in which it has relatively high solubility is methanol (≥ 30 mg/mL).

CLINICAL TRIALS

Efficacy Studies

Study demographics and trial design

Table 4: Summary of patient demographics for clinical trials in ADHD					
Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
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 4mg, once daily, 8 weeks	345 (6-12 yrs: 265) (13-17yrs: 80)	10.5 yrs (6-17)	257M: 88F
Study 2*	Randomized, double-blind, placebo-controlled, forced-dose study conducted in children and adolescents aged 6-17 years with ADHD	Oral, 1, 2, 3 and 4mg, 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, 7mg, 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 4mg, 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

*Only patients weighing <110lbs could be randomized to 1mg.

The efficacy of INTUNIV XR 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- 4mg for children and 1-7mg in adolescents.

In Study 4, the safety and efficacy of INTUNIV XR 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 dexamethylphenidate 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 INTUNIV XR 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).

Study results

Short-Term Monotherapy Trials

Table 5: 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*	ADHD Rating Scale (ADHD-RS-IV) total score change from baseline to endpoint for the ITT population	Mean (SD) 2mg: -15.40 (12.82) 3mg: -15.79 (13.00) 4mg: -18.96 (13.71) Comparison (placebo-adjusted difference)*** 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**	ADHD Rating Scale (ADHD-RS-IV) total score change from baseline to endpoint for the ITT population	Mean (SD) 1mg: -20.4 (14.00) 2mg: -18.0 (14.88) 3mg: -19.4 (14.62) 4mg: -20.9 (11.89) Comparison (placebo-adjusted difference)*** 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)

*p-value and 95% CI from Dunnett's adjustment for multiple means comparisons

**Only patients weighing <110lbs could be randomized to 1mg

***Age subgroup analysis revealed statistically significant efficacy for only children aged 6 to 12 years

ITT: Intent to Treat

FAS: Full analysis set

In Study 1, the improvement in ADHD-RS-IV total scores at endpoint in all randomized INTUNIV XR treatment groups was statistically significantly greater than in placebo treatment groups (p<0.001) for each of the 2mg, 3mg, and 4mg INTUNIV XR randomized treatment groups. Improvements in ADHD-RS-IV scores were observed in patients taking INTUNIV XR 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 INTUNIV XR treatment groups compared to the placebo treatment

groups ($p < 0.02$) for each of the 2mg, 3mg, and 4mg INTUNIV XR randomized treatment groups, and for the 1mg 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 INTUNIV XR 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.

Short-Term Adjunctive Trial

Table 6: Results of Study 4 in ADHD (Children and Adolescents aged 6-17 years)		
Primary Endpoints	Associated value and statistical significance for Drug+ Psychostimulant at all dosages	Associated value and statistical significance for Placebo
ADHD Rating Scale (ADHD-RS-IV) total score change from baseline to endpoint for FAS population	Mean (SD) All doses AM: -20.4 (12.77) All doses PM: -21.0 (12.39) Overall: -20.7 (12.56) Comparison (placebo-adjusted difference) LS mean ¹ (95% CI) -4.5 (-7.5, -1.4) p=0.002 ² -5.3 (-8.3, -2.3) p<0.001 ² -4.9 (-7.2, -2.6) p<0.001 ³	Mean (SD) -16.0 (11.77)

FAS – Full analysis set

¹LS 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.

² p-value of INTUNIV XR AM and PM groups based on Dunnett's multiple comparison procedure.

³ p-value for all INTUNIV XR was a t-test. This was a secondary efficacy analysis.

Mean reductions in ADHD-RS-IV total scores at endpoint were significantly greater for INTUNIV XR 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 INTUNIV XR 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 INTUNIV XR taken in the morning (AM), and 83.1% for INTUNIV XR in the evening (PM) group. The results indicated a statistically significant difference from placebo in the evening (PM) INTUNIV XR dosing group but not the morning (AM) INTUNIV XR 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.

DETAILED PHARMACOLOGY

Safety Pharmacology

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.

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.

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.

Pharmacokinetics

Guanfacine is rapidly and well absorbed in rat and dog after oral administration. In rats, the absorbed drug was widely distributed in various tissues including the brain, the fetuses of pregnant rats and the milk of lactating rats. Plasma protein binding was moderate, amounting to approximately 71% in rat plasma.

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.

After oral or intravenous administration of the [14C]-labelled drug, radioactivity was excreted equally in urine and feces of rats, although urinary excretion was more important in dogs. Biliary excretion and recirculation were extensive in rats. Relatively little unchanged parent drug was found in rat urine. In dogs, about ¼ of the radioactivity in urine was the unchanged drug. No radioactivity was found in the expired air of the rat. The pattern of metabolism and excretion of radioactivity was not altered by repeated dosing. No accumulation of the drug and/or its metabolites was evident in these animal studies.

Guanfacine did not inhibit cytochromes P450 CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 in vitro, and is therefore unlikely to affect the in vivo clearance of other co-administered drugs metabolised by cytochrome P450s. Guanfacine is primarily metabolised by CYP3A4 in human liver microsomes, and has been studied in a clinical study (see **Drug Interactions, Drug-Drug Interactions - CYP3A4 and CYP3A5 Inhibitors, and CYP3A4 Inducers**).

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 0.12mg/kg/day on a mg/m² 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/m² 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 0.12mg/kg/day on a mg/m² 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.

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PART III: CONSUMER INFORMATION

PrINTUNIV XR®*

guanfacine hydrochloride extended-release tablets

This leaflet is part III of a three-part "Product Monograph" published when INTUNIV XR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INTUNIV XR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- INTUNIV XR may be a part of the patient's overall treatment of ADHD. The doctor may also recommend that you/your child have/has counselling or other therapy.
- INTUNIV XR is a prescription medicine, specifically a selective alpha_{2A}-adrenergic receptor agonist. It contains guanfacine hydrochloride which is used to treat the symptoms of Attention Deficit Hyperactivity Disorder (ADHD) in children 6-17 years of age.

What it does:

INTUNIV XR helps increase attention (including the ability to follow directions and finish tasks) and decrease impulsiveness and hyperactivity in patients with ADHD.

When it should not be used:

INTUNIV XR should not be taken if

- You/your child are/is allergic to guanfacine or any other non-medicinal ingredients in INTUNIV XR. (see What the non-medicinal ingredients are)
- Your child is younger than 6 years old.

What the medicinal ingredient is:

guanfacine hydrochloride

What the non-medicinal ingredients are:

Crospovidone, fumaric acid, glyceryl behenate, green pigment blend PB-1763 (3mg and 4mg tablets only), hypromellose, lactose, methacrylic acid copolymer, microcrystalline cellulose, and povidone.

What dosage forms it comes in:

Tablets; 1mg, 2mg, 3mg, and 4mg guanfacine as guanfacine hydrochloride

WARNINGS AND PRECAUTIONS

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

Mental (Psychiatric) problems:

- New or worse thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide actions (suicide attempt, completed suicide)
- New or worse bipolar illness, characterized by 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)
- New or worse aggressive behavior or hostility
- New psychosis (such as hearing voices, believing things that are not true, are suspicious) or new mania (unusually excited, over-active or un-inhibited).

These new or worse mental problems may be more likely to occur if your child has mental disorders that you may or may not know about. Tell your child's doctor about any mental problems your child has, or about any personal or family history of suicide, bipolar illness, or depression.

A small number of patients taking ADHD drugs may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of suicide, self-harm or harm to others. Those suicidal thoughts or behaviors may occur at any time *during* treatment, particularly at the start or during dose changes, and also *after stopping* INTUNIV XR. **Should this happen to your child, talk to your child's doctor immediately. Close observation by a doctor is necessary in this situation.**

Call your child's doctor right away if your child has any new or worsening mental symptoms while taking INTUNIV XR, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

BEFORE you/your child uses INTUNIV XR, talk to your doctor or your child's doctor or pharmacist if you/your child:

- Have/has a heart problem (e.g., very low heart rate (pulse), heart rhythm problem)
- Have/has already fainted in the past (or have/has a history of fainting)
- Have/has low or high blood pressure
- Have/has liver or kidney problems
- Have/has mental problems or a family history of mental problems including psychosis, mania, bipolar illness, depression, or suicide

- Have/has any other medical condition
- Are/ is pregnant
- Are/is breast-feeding or plans to breast-feed

While on INTUNIV XR, you/your child should avoid becoming dehydrated or overheated.

Talk to your doctor or your child's doctor or pharmacist about any problem with weight while taking INTUNIV XR.

Do not drive, operate heavy machinery, or do other dangerous activities until you know how INTUNIV XR affects you. INTUNIV XR can slow your thinking and motor skills. INTUNIV taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

INTERACTIONS WITH THIS MEDICATION

It is important to tell your doctor or your child's doctor or pharmacist about all medicines that you/your child are/ is taking, including medicines prescribed by other doctors, medicines or vitamins that you buy without a prescription, and any other alternative medicines and herbal remedies. While on INTUNIV XR, do not take/give your child a new medicine or herbal remedy before checking with your doctor or your child's doctor.

It is especially important to inform your doctor or your child's doctor if you or your child takes the following medication:

- Medicines that can affect enzyme metabolism (such as ketoconazole, rifampin)
- Valproic acid
- Medicines that affect heart functioning (e.g., QT interval-prolongation, pulse and blood pressure)
- Drugs causing 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)
- Medication used to manage psychosis (antipsychotics)
- Alcohol
- Other medicines for ADHD
- Any drug that may cause heart valve problems

Know the medicines that you/your child takes. Keep a list of you/your child's medicines with you to show the doctor and pharmacist each time you/your child have/has an appointment.

PROPER USE OF THIS MEDICATION

- You/your child should take INTUNIV XR exactly as your doctor or your child's doctor prescribes.
- You/your child should not stop taking INTUNIV XR without talking to your doctor or your child's doctor.
- INTUNIV XR should be taken once a day, either alone or with an ADHD psychostimulant medication prescribed by your doctor or your child's doctor. This doctor will tell you when you/your child should take INTUNIV XR and when to take your/his/her ADHD psychostimulant medication.
- Do not take INTUNIV XR with a high-fat meal.

Usual dose:

The recommended starting dose is 1mg tablet once a day. To be swallowed whole with a small amount of liquid. Should not be crushed, chewed, broken or divided prior to swallowing-

The increments of dosage should be no more than 1mg per week. Total daily dose between 1-7mg.

In order to receive the most benefit from INTUNIV XR, it is important that INTUNIV XR be taken only as directed by your doctor or your child's doctor. The doctor may adjust the amount of drug taken until it is right for you/your child.

Overdose:

In case of drug overdose, contact a health care practitioner, 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 (bradycardia), sleepiness (lethargy), and difficulty breathing (respiratory depression).

Children/adolescents who develop lethargy should be observed for the development of more serious symptoms including, slowing of heart rhythm and low blood pressure due to the possibility of delayed onset of these symptoms.

Missed Dose:

If two or more consecutive doses are missed, talk to your doctor or your child's doctor. It is recommended to have your doctor or your child's doctor restart you/your child on the lowest possible dose.

Discontinuation:

You/your child should not stop taking INTUNIV XR without talking to your doctor or your child's doctor about how to stop the medicine. Sudden discontinuation of INTUNIV XR may lead to serious increase in blood pressure and heart rate (pulse).

Withdrawal symptoms of high blood pressure and increased heart rate after suddenly stopping INTUNIV XR may occur within a few days or after a few weeks and may be accompanied by headaches, feeling confused, nervousness, agitation, and tremors; and may require immediate medical assistance.

These effects on blood pressure and heart rate may be more important if you/your child are taking a psychostimulant in addition to INTUNIV XR.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its desired effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur, talk to your doctor or your child's doctor.

The most common side effects include:

- Sleepiness, trouble sleeping
- Tiredness, dizziness
- Headache
- Nausea, stomach pain
- Decreased appetite

You/your child should avoid performing tasks which may require special attention, such as driving, riding a bike, operating machinery or doing other dangerous activities until you/they are certain that INTUNIV XR does not adversely affect you/them.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Seek immediate medical help
		Only if severe	In all cases	
Common	Low blood pressure Sleepiness		√	
Uncommon	Low heart rate (pulse) Fainting Convulsion		√ √ √	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Seek immediate medical help
Unknown	Allergic reaction: rash, itching, hives, swelling of the face, nose, lips or tongue, difficulty breathing or swallowing, dizziness			√
	New Psychotic or Manic Symptoms: -Paranoia, delusions Hallucinations: seeing, feeling or hearing things that are not real Mania: feeling unusually excited, over-active, or uninhibited (see Warnings and Precautions)		√ √ √	
	Aggressive Behavior or Hostility		√	
	Suicidal Behavior: Thoughts or actions about hurting or killing yourself. (see Warnings and Precautions)			√
	High Blood Pressure after suddenly stopping INTUNIV XR: headaches, feeling confused, nervousness, agitation, tremors			√

This is not a complete list of side effects. For any unexpected effects while taking INTUNIV XR, contact your doctor or your child's doctor or pharmacist.

HOW TO STORE IT

Store at 25°C (77°F); excursions permitted from 15° to 30°C (59° to 86°F). Keep out of sight and reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at
www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at
www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION**If you want more information about INTUNIV XR:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website <http://hc-sc.gc.ca>, the manufacturer's website www.shirecanada.com, or by calling 1-800-268-2772.

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