AUSTRALIAN PRODUCT INFORMATION

INTUNIV® (guanfacine hydrochloride)

1 NAME OF THE MEDICINE

Guanfacine hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

INTUNIV modified release tablet contains guanfacine hydrochloride equivalent to 1 mg, 2 mg, 3 mg, or 4 mg of guanfacine base.

INTUNIV (guanfacine hydrochloride) was developed as a tablet for once-a-day oral administration. The chemical designation for guanfacine hydrochloride is N-(diaminomethylidene)-2-(2,6-dichlorophenyl) acetamide hydrochloride. Guanfacine hydrochloride is a white to off-white crystalline powder that is sparingly soluble in water. Guanfacine hydrochloride has a 2-octanol/water partition coefficient (logP) of 0.10; a dissociation constant of 7.69; and pH of ~4 when dissolved in water.

The modified release tablets of guanfacine hydrochloride are designed such that the drug is released slowly, absorbed over an extended period of time, thereby reducing peak plasma levels; therefore, the tablets should not be crushed or altered.

Excipients with known effect: lactose.
For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Modified release tablets.

Appearance

INTUNIV 1 mg modified release tablet: round, white to off-white tablets debossed with '1MG' on one side and '503' on the other side.

INTUNIV 2 mg modified release tablet: oblong-shaped, white to off-white tablets debossed with '2MG' on one side and "503" on the other side.

INTUNIV 3 mg modified release tablet: round, green tablets debossed with '3MG' on one side and '503' on the other side.

INTUNIV 4 mg modified release tablet: oblong-shaped, green tablets debossed with '4MG' on one side and '503' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

INTUNIV is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants).

INTUNIV must be used as part of a comprehensive ADHD management programme, typically including psychological, educational and social measures.

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of administration

INTUNIV is a modified-release tablet and is taken once daily either morning or evening.

INTUNIV should not be crushed, chewed, or broken before swallowing because this increases the rate of guanfacine release. INTUNIV should not be administered with high fat meals, due to increased exposure, as it has been shown that high fat meals have a significant effect on the absorption of guanfacine. INTUNIV should not be administered together with grapefruit juice.

Dosage in paediatric patients (children and adolescents)

The recommended starting dose for INTUNIV is 1 mg, taken orally once a day, for both monotherapy and when co-administered with psychostimulants.

The dose is adjusted in increments of no more than 1 mg/week for both monotherapy and when co-administered with psychostimulants.

In monotherapy clinical trials, there was dose- and exposure-related clinical improvement as well as risks for several clinically significant adverse reactions (hypotension, bradycardia, sedative events). To balance the exposure-related potential benefits and risks, the recommended maintenance dose range depending on clinical response and tolerability for INTUNIV is 0.05-0.12 mg/kg/day (total daily dose between 1-7 mg. See Table 1).

Table 1: Recommended Target Dose Range for Maintenance Therapy with INTUNIV

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
58.5-91.0 kg	4-7 mg/day
≥91.0 kg	5-7 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 co-administration trial which evaluated INTUNIV treatment with psychostimulants, the majority of subjects reached optimal doses in the 0.05-0.12 mg/kg/day range. Doses above 4 mg/day have not been studied in co-administration trials and therefore are not recommended.

Long-term use

Pharmacological treatment of ADHD may be needed for extended periods. The benefit of maintaining children and adolescent patients (6-17 years) with ADHD on INTUNIV was demonstrated in a controlled randomised withdrawal trial (see Section 5.1 PHARMACODYNAMIC PROPERTIES/CLINICAL TRIALS). The majority of children and adolescents reached optimal doses in the 0.05-0.12 mg/kg/day range. Doses above 4 mg/day have not been evaluated in children (ages 6-12 years) and above 7 mg/day have not been evaluated in adolescents (ages 13-17 years).

The clinician who elects to use INTUNIV for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Missed doses

In the event of a missed dose, INTUNIV dosing can resume the next day. If two or more consecutive doses are missed, re-titration is recommended based on the patient's tolerability to INTUNIV.

Downward titration and discontinuation

Patients/caregivers should be instructed not to discontinue INTUNIV 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. Blood pressure and pulse should be monitored when reducing the dose or discontinuing INTUNIV (See Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.8 ADVERSE EFFECTS).

Tapering INTUNIV dosing during withdrawal is recommended to minimise these potential withdrawal effects.

Sub-optimal responders to psychostimulants

INTUNIV may be co-administered with psychostimulants in patients in whom psychostimulants alone have not provided an adequate response (see Section 5.1 PHARMACODYNAMIC PROPERTIES/CLINICAL TRIALS). Dosing should follow the recommended doses as described above.

The recommended maintenance dose for INTUNIV when co-administered with psychostimulants is within the range of 1-4 mg/day, depending on clinical response and tolerability. Doses above 4 mg/day have not been evaluated in co-administration trials (see Section 5.1 PHARMACODYNAMIC PROPERTIES/CLINICAL TRIALS).

4.3 CONTRAINDICATIONS

INTUNIV is contraindicated in patients with a history of hypersensitivity to INTUNIV, its excipients, or other products containing guanfacine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

INTUNIV can cause syncope, hypotension, and bradycardia.

In short-term paediatric monotherapy and co-administration trials, dose-dependent decreases in mean heart rate (6-9 bpm) and decreases in mean blood pressure (systolic [4-5 mm/Hg] and diastolic [3 mm/Hg]) were observed.

In long-term, monotherapy, open-label studies (mean exposure of approximately 10 months), maximum decreases in systolic and diastolic blood pressure occurred in the first month of therapy. The majority of syncope cases occurred in the long-term, open-label studies.

Measure patients' heart rates and blood pressures prior to initiation of treatment, following dose increases, and periodically while on therapy.

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 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 can decrease blood pressure and heart rate. Caution is advised when treating patients with INTUNIV 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 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION/Antihypertensive Drugs). Patients/caregivers should be advised that patients should avoid becoming dehydrated or overheated.

Sedation and somnolence

INTUNIV may cause somnolence and sedation. Before INTUNIV is used with other centrally active depressants (such as alcohol, sedatives, hypnotics, antipsychotics, phenothiazines, barbiturates, or benzodiazepines), the potential for additive sedative effects should be considered. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with INTUNIV. Patients should avoid use with alcohol.

Use caution when INTUNIV 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.

Effects on height, weight and body mass index (BMI)

Children and adolescents treated with INTUNIV may show an increase in their BMI. Therefore, monitoring of height, weight and BMI should be done prior to initiation of therapy and then every 3 months for the first year, taking into consideration clinical judgement. 6 monthly monitoring should follow thereafter, with more frequent monitoring following any dose adjustment.

Rebound effects (Blood pressure and heart rate increase) upon discontinuation or treatment interruption

Blood pressure and pulse may increase following discontinuation of INTUNIV.

Abrupt discontinuation of INTUNIV can lead to clinically significant and persistent rebound hypertension. In the post-marketing setting, cases of rebound hypertension including hypertensive encephalopathy have been reported rarely following discontinuation or treatment interruption. (see Section 4.8 ADVERSE EFFECTS) Concomitant stimulant use was also reported, which may potentially increase the hypertensive response upon abrupt discontinuation of guanfacine.

Caution is recommended in children who have gastrointestinal illnesses that lead to vomiting because the resulting inability to take medications may lead to a risk of guanfacine rebound effects.

To minimize the risk of an increase in blood pressure upon discontinuation, the total daily dose of INTUNIV should be tapered in decrements of no more than 1 mg every 3 to 7 days (see Section 4.2 DOSAGE AND METHOD OF ADMINISTRATION). Blood pressure and pulse should be monitored when reducing the dose or discontinuing INTUNIV.

Use in hepatic impairment

Guanfacine is cleared by the liver, and approximately 50% of the clearance of guanfacine is hepatic. Dose reduction may be required in patients with different degrees of hepatic impairment. The impact of hepatic impairment on the pharmacokinetics of guanfacine in paediatric patients (children and adolescents 6-17 years old inclusive) has not been assessed.

Use in renal impairment

Guanfacine is also cleared by the kidneys, with approximately 30% of the drug excreted unchanged in the urine. Dose reduction may be required in patients with severe renal impairment (GFR 29-15 ml/min) and an end stage renal disease (GFR<15 ml/min) or requiring dialysis. The impact of renal impairment on the pharmacokinetics of guanfacine in paediatric patients (children and adolescents 6-17 years old) has not been assessed.

Use in adults and the elderly

The safety and efficacy of guanfacine in adults and the elderly with ADHD has not been established and therefore guanfacine should not be used in this group.

Paediatric use

Paediatric patients taking INTUNIV demonstrated similar growth compared to normative data.

The safety and efficacy of INTUNIV in paediatric patients less than 6 years of age have not been established.

Studies using juvenile rats showed that co-administration of guanfacine and methylphenidate increased plasma exposure values (both C_{max} and AUC) for the former by a factor of approximately 2–4 (as cf. administration of guanfacine alone) but had no effect on exposure values for the latter compound. The basis for this effect on guanfacine exposure is not known.

Effects on laboratory tests

No data available.

Abuse and dependence

INTUNIV has no known potential for abuse or dependence.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

CYP3A4 and CYP3A5 Inhibitors

Use caution when INTUNIV is administered to patients taking ketoconazole and other moderate and strong CYP3A4/5 inhibitors, 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 increased 3-fold (area under the curve [AUC]).

CYP3A4 Inducers

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

Transporters

Guanfacine is an *in vitro* inhibitor of MATE1 and the clinical relevance of MATE1 inhibition cannot be excluded. Concomitant administration of guanfacine with MATE1 substrates may result in increases in the plasma concentrations of these medicinal products. Furthermore, 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.

Valproic Acid

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

Antihypertensive Drugs

Use caution when INTUNIV is administered concomitantly with antihypertensive drugs, due to the potential for additive pharmacodynamic effects such as hypotension and syncope.

Oral Methylphenidate

In a drug interaction study, neither INTUNIV nor methylphenidate HCl modified-release were found to affect the pharmacokinetics of the other drug when taken in combination.

Lisdexamfetamine Dimesylate

In a drug interaction study, administration of INTUNIV in combination with lisdexamfetamine dimesylate 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 co-administration of INTUNIV and lisdexamfetamine dimesylate.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No adverse effects were observed in fertility studies in male and female mice and rats given oral doses up to 22 times the maximum recommended human dose (MRHD) of 0.12 mg/kg/day on a mg/m^2 basis. Exposures achieved in these studies were not measured but likely to be similar to clinical exposure at the MRHD.

Use in pregnancy

(Category B3)

There are no adequate, well-controlled studies of INTUNIV in pregnant women. INTUNIV should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.

Rat experiments have shown that guanfacine crosses the placenta. Oral administration of guanfacine to rats and rabbits at about 4 and 3 times, respectively, the maximum recommended human dose (MRHD) of 0.12 mg/kg/day on a mg/m2 basis, resulted in no evidence of harm to the foetus. Higher doses (14 times or greater the MRHD were associated with reduced foetal survival and maternal toxicity in both species. Exposures achieved in these studies were not measured but likely to be similar to clinical exposure at the MRHD.

Use in lactation

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

Oral administration of guanfacine to rats from late gestation to weaning at about 6 times the maximum recommended human dose (MRHD) of 0.12 mg/kg/day on a mg/m^2 basis did not affect pup development. Higher doses were associated with reduced pup weight and pup mortality. Exposures achieved in these studies were not measured but likely to be similar to clinical exposure at the MRHD.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

However, patients should be advised that treatment with INTUNIV can cause dizziness, sedation, fatigue and somnolence. These effects occur predominantly at the start of treatment and may occur less frequently as treatment continues. Syncope has also been observed in patients receiving treatment with INTUNIV.

If patients experience the above mentioned side effects, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Drug Reactions (ADRs) Reported with INTUNIV

Table 2 presents all Adverse Drug Reactions based on all safety information available, sorted by MedDRA SOC and decreasing categories of frequency.

Table 2. Adverse Drug Reactions Reported with INTUNIV

System/Organ Class Adverse Drug Reaction	**INTUNIV Monotherapy Trials (n = 1419)***	**INTUNIV Co-administration Trial (n = 302)***
Immune System Disorders		
Hypersensitivity	Uncommon	Not Reported
Metabolism and Nutrition Disorders		
Decreased appetite	Common	Common
Psychiatric Disorders		
Insomnia	Common	Very Common
Anxiety	Common	Common
Affect lability	Common	Common
Middle insomnia	Common	Common
Nightmare	Common	Common
Depression	Common	Uncommon
Agitation	Uncommon	Not Reported
Nervous System Disorders		
Somnolence	Very Common	Very Common
Headache	Very Common	Very Common
Sedation	Common	Common
Dizziness	Common	Common
Lethargy	Common	Common
Syncope/loss of consciousness	Uncommon	Uncommon
Dizziness postural	Uncommon	Common
Convulsion	Uncommon	Not Reported
Hypersomnia	Rare	Uncommon
Cardiac Disorders		
Bradycardia	Common	Common
Tachycardia	*Uncommon*	*Common*
Sinus arrhythmia	Uncommon	Not Reported
Atrioventricular block first degree	Uncommon	Not Reported
Vascular Disorders		
Hypotension	Common	Uncommon
Orthostatic hypotension	Common	Common
Pallor	Uncommon	Uncommon
Hypertension	Rare	Not Reported
Hypertensive encephalopathy	*Not reported*[a]	*Not reported*[a]
Respiratory, Thoracic, and Mediastinal Disorders		
Asthma	Uncommon	Common
Gastrointestinal Disorders		
Abdominal pain	Very Common	Common
Nausea	Common	Common
Vomiting	Common	Common
Diarrhoea	Common	Common
Dry mouth	Common	Common
Constipation	Common	Common
Abdominal/stomach discomfort	Common	Common
Dyspepsia	Uncommon	Not Reported
Skin and Subcutaneous Tissue Disorders		
Rash	*Common*	*Common*
Pruritis	*Uncommon*	*Uncommon*
Renal and Urinary Disorders		

Enuresis	Common	Common
Pollakiuria	Uncommon	Uncommon
Reproductive System and Breast Disorders		
Erectile dysfunction	*Not reported*	*Not reported*
General Disorders		
Fatigue	Very Common	Common
Irritability	Common	Common
Asthenia	Uncommon	Uncommon
Chest pain	Uncommon	Not Reported
Investigations		
Blood pressure decreased	Common	Not Reported
Weight increased	Common	Uncommon
Heart rate decreased	Uncommon	Uncommon
Alanine aminotransferase increased	Uncommon	Not Reported
Blood pressure increased	Uncommon	Not Reported

*Incidence category: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to <1/1,000)
The table presents data from completed clinical trials with INTUNIV (n = 1721). This includes INTUNIV monotherapy trials and a co-administration trial with psychostimulants.
ADRs from post marketing experience are *italicised*.
[a] Reported very rarely (<1 in 1,000,000) in postmarketing experience.

Description of Selected Adverse Drug Reactions (ADRs)

Rebound effects (Blood Pressure and Heart Rate Increase) upon discontinuation or treatment interruption of INTUNIV:
Blood pressure and pulse may increase following discontinuation of INTUNIV. In postmarketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation of INTUNIV (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In a maintenance of efficacy study in children and adolescents, increases in mean systolic and diastolic blood pressure, of approximately 3 mmHg and 1 mmHg respectively, above original baseline were observed upon discontinuation of INTUNIV. The increases in blood pressure were observed in some individuals at the end of the follow up period which ranged between 3 and 26 weeks post final dose. 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 INTUNIV and then decreased to baseline 4 weeks later. In this study, the increases in blood pressure and pulse were not considered serious or associated with adverse events. However, individuals may have larger increases than reflected by the mean changes (see Section 5.1 PHARMACODYNAMIC PROPERTIES/CLINICAL TRIALS).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and symptoms of overdose may include hypotension, initial hypertension, bradycardia, lethargy, and respiratory depression. Management of INTUNIV overdose should include

monitoring for and treatment of these signs and symptoms. Paediatric patients (children and adolescents 6-17 years old inclusive) 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 information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Guanfacine is a selective alpha$_{2A}$-adrenergic receptor agonist. Guanfacine is not a central nervous system (CNS) stimulant, a monoamine transporter inhibitor or releaser of pre-synaptic dopamine or norepinephrine. The mode of action of guanfacine in ADHD is not fully established. Preclinical research suggests guanfacine modulates signalling in the prefrontal cortex and basal ganglia through direct modification of synaptic norepinephrine transmission at the alpha 2-adrenergic receptors.

Pharmacodynamic effects

Guanfacine is a selective alpha$_{2A}$-adrenergic receptor agonist in that it has 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.

In a thorough QT study, the administration of two dose levels of immediate-release guanfacine (4 mg and 8 mg) produced concentrations approximately 2 to 4 times the concentrations observed with the maximum recommended dose of INTUNIV of 0.12 mg/kg. Guanfacine was not shown to prolong the QTc interval to any clinically relevant extent.

Clinical trials

The effects of INTUNIV in the treatment of ADHD has been demonstrated in 5 controlled studies in children and adolescents (6 to 17 years), 3 short term controlled trials in children and adolescents aged 6 to 17 years, 1 short-term controlled study in adolescents aged 13 to 17 years, and 1 randomised withdrawal trial in children and adolescents aged 6-17, all of whom met the DSM-IV-TR criteria for ADHD. The majority of patients achieved an optimised dose between 0.05-0.12mg/kg/day.

Monotherapy studies in ADHD patients

Fixed-dose studies

The efficacy of INTUNIV in the treatment of ADHD was established in 2 randomised, double-blind, placebo-controlled, fixed-dose (range of 1-4 mg/day) monotherapy trials in paediatric patients (children and adolescents 6-17 years old inclusive). Studies SPD503-301 (n = 345) and SPD503-304 (n = 324) were 8 and 9 weeks in duration, respectively. Signs and symptoms of ADHD were evaluated as the change from baseline to endpoint in ADHD Rating Scale (ADHD-RSIV) scores. In both studies, patients were randomized to 2 mg, 3 mg or 4 mg dose groups, titrated to their target fixed dose, and continued on the same dose until a dose tapering phase started. The lowest dose of 1 mg used in Study SPD503-304 was assigned only to patients less than 50 kg. Patients who weighed less than 25 kg were not included in either study.

Dose-responsive efficacy was evident, particularly when data were examined on a weight adjusted (mg/kg) basis. When evaluated over the dose range of 0.01-0.17 mg/kg/day, clinically relevant improvements were observed beginning at doses in the range of 0.05-0.08 mg/kg/day. If well-tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit. INTUNIV showed significantly greater improvement compared to placebo on the change from baseline to final on treatment assessment in the ADHD Rating Scale (ADHD-RS-IV) score in both studies (placebo-adjusted reduction in LS mean range from 5.4 to 10.0, $p<0.02$).

Dose-Optimisation Studies

AM/PM Dosing Study
SPD503-314 was a 9-week, double-blind, randomised, placebo-controlled, dose-optimisation study conducted in children aged 6-12 years (n = 340) to assess the efficacy of once daily dosing with INTUNIV (1-4 mg) administered either in the morning or the evening. Symptoms of ADHD were evaluated as the change from baseline to week 8 (final on treatment assessment) in the ADHD Rating Scale (ADHD-RS-IV) total scores. INTUNIV showed significantly greater improvement compared to placebo regardless of time (AM or PM) of administration (placebo-adjusted LS mean difference of -9.4 and -9.8 for AM and PM dosing, respectively, $p<0.001$).

ADHD with Oppositional Symptoms Study
SPD503-307 was a 9-week, double-blind, randomised, placebo-controlled, dose-optimisation study with INTUNIV (1-4 mg/day) conducted in children aged 6-12 years with ADHD and oppositional symptoms (n = 217), as measured by the change from baseline score on the oppositional subscale of the Conner's Parent Rating Scale – Revised Long Form (CPRS-RL). Results show statistically significantly ($p\leq0.001$) greater mean reductions at endpoint from Baseline (indicating improvement) in oppositional subscale of CPRS-R:L scores in the guanfacine group compared to placebo (10.9 points vs. 6.8 for guanfacine vs. placebo, respectively) and the effect size was 0.6 ($p<0.001$). These reductions represent a percentage reduction of 56% vs. 33% for guanfacine vs. placebo, respectively. In addition, symptoms of ADHD were evaluated as the change from baseline to final on treatment assessment in the ADHD Rating Scale (ADHD-RS-IV) total scores. INTUNIV showed significantly greater ($p < 0.001$) improvement compared to placebo.

Adolescents
SPD503-312 was a 15-week, double-blind, randomised, placebo-controlled, dose-optimisation study conducted in adolescents aged 13-17 years (n=314) to confirm the

efficacy, safety, and tolerability of INTUNIV (1-7 mg/day; optimised dose range of 0.05-0.12 mg/kg/day) in the treatment of ADHD as measured by the ADHD Rating Scale-IV (ADHD-RS-IV). Subjects receiving INTUNIV showed significantly greater improvement on the ADHD-RS-IV total score compared with subjects receiving placebo ($p<0.001$). Guanfacine-treated patients were in statistically significantly better conditions on the functional outcome as measured by the clinical global impression of severity (CGI-S) at endpoint compared to placebo-treated patients. Superiority (statistical significance) over placebo on the family and school, and learning domains of the WFIRS-P score was not established in this study.

Children and adolescents
SPD503-316 was a 12-week (6-12 years) or 15-week (13-17 years), randomised, double-blind, parallel-group, placebo- and active-reference (STRATTERA®), dose optimisation study conducted in paediatric patients (children and adolescents aged 6-17 years old inclusive) (n=337) to assess the efficacy and safety of once-daily dosing (children: 1-4 mg/day, adolescents: 1-7 mg/day; optimised dose range of 0.05 to 0.12 mg/kg/day) in the treatment of ADHD. INTUNIV was superior to placebo on symptoms of ADHD in subjects 6-17 years as measured by change from baseline in ADHD-RS-IV total scores ($p<0.001$).

The ADHD Rating Scale is a measure of the core symptoms of ADHD. The results with respect to the primary endpoint study are presented in Table 3.

Table 3. Summary of primary efficacy for study SPD503-316: ADHD-RS-IV

Treatment groups	**N**	**Baseline ADHD-RS-IV (SD)**	**Change from baseline (SD)**	**Difference from placebo (95%CI) Effect size**	**Responders**	**Difference from placebo (95%CI)**
Guanfacine	114	43.1 (5.5)	-23.9 (12.4)	-8.9 (-11.9, -5.8) 0.8	64.3%	21.9% (9.2 ; 34.7)
Atomoxetine	112	43.7 (5.9)	-18.6 (11.9)	-3.8 (-6.8, -0.7) 0.3	55.4%	13.0% (0.0 ; 26.0)
Placebo	111	43.2 (5.6)	-15.0 (13.1)	NA	42.3%	NA

Results of the secondary endpoints were consistent with that of the primary endpoint. The percentages of subjects who met response criteria (≥30% reduction from baseline in ADHD-RS-IV Total Score and a CGI-I value of 1 or 2) was 64.3% forINTUNIV, 55.4% for atomoxetine and 42.3% for placebo. Guanfacine also showed significant improvement in learning, school and family functioning as measured with the (WFIRS-P score).

SPD503-316 was not intended either as a superiority or non-inferiority study and no conclusions with regard to superiority or equivalence can be made from the study.

Long-Term Maintenance of Efficacy Study
SPD503-315 was a 41-week long-term maintenance of efficacy study, with an open-label phase (up to 13 weeks) followed by a 2-week blinded taper and a placebo-controlled, randomised-withdrawal phase (up to 26 weeks), conducted in paediatric patients (children and adolescents aged 6-17 years old inclusive) (n=526 in the open-label phase and n=315 in the double-blind randomised-withdrawal phase) to assess the efficacy, safety, and tolerability of once-daily dosing with INTUNIV (children: 1-4 mg/day, adolescents: 1-7 mg/day; optimised dose range of 0.05 to 0.12 mg/kg/day) in the treatment of ADHD. INTUNIV was superior to placebo in the long-term maintenance of treatment in children and adolescents with ADHD as measured by cumulative treatment failures (49.3% for Intuniv, and 64.9% for placebo, $p=0.006$). Treatment failure was defined as a ≥ 50% increase (worsening) in ADHD-RS-IV total score and a ≥ 2-point increase in CGI-S score compared to the respective scores

at the double-blind baseline visit. A subject who met the treatment failure criteria on two consecutive visits or discontinued for any reason was identified (or included) as a treatment failure.

Cognitive Function Study

SPD503-206 was a 15-week, double-blind, dose-optimisation, safety and tolerability study conducted in paediatric patients (children and adolescents 6-17 years old inclusive) (n = 182) comparing the effects of INTUNIV (1-3 mg) to placebo on the Choice Reaction Time Test (Cambridge Neuropsychological Test Automated Battery - CANTAB). There was no evidence of impairment in speed processing compared to placebo.

Co-administration with psychostimulants study

Dose-Optimisation Study

SPD503-313 was a 9-week, double-blind, placebo-controlled, dose-optimisation, co-administration study conducted in paediatric patients (children and adolescents aged 6-17 years old inclusive) with a diagnosis of ADHD and a sub-optimal response to stimulants. The safety and efficacy of INTUNIV (1-4 mg/day) were evaluated when co-administered with psychostimulants (longer-acting formulations of mixed salts of a single-entity amphetamine product, lisdexamfetamine dimesylate, methylphenidate HCl, and dexmethylphenidate HCl). Patients continued to take their psychostimulant in the morning and were dosed either in the morning or the evening with INTUNIV (1-4 mg/day) or with placebo in addition to their psychostimulant.

The majority of subjects reached optimal doses in the 0.05-0.12 mg/kg/day range.

Symptoms of ADHD were evaluated as the change from baseline to endpoint (Week 8 LOCF) in ADHD Rating Scale (ADHD-RS-IV) total scores. The mean reductions in ADHD-RS-IV total scores at endpoint were significantly greater for INTUNIV co-administered with a psychostimulant compared to placebo taken with a psychostimulant (20.7 (12.6) points vs. 15.9 (11.8); difference: 4.9 95% CI 2.6, 7.2). This result was consistent for both AM and PM dosing ($p = 0.002$ for placebo vs AM and $p < 0.001$ for placebo vs PM, applying Dunnett's adjustment). No age differences were observed with respect to response to the ADHD-RS-IV.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Guanfacine is readily absorbed, with peak plasma concentrations reached approximately 5 hours after oral administration of INTUNIV to paediatric patients (children and adolescents 6-17 years old inclusive). In adults, the mean exposure to guanfacine increased (~ 75% increase for C_{max} and ~ 40% for AUC) when taken together with a high fat meal, compared to intake in the fasted state.

Distribution

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

Metabolism

In vitro studies with human liver microsomes and recombinant CYPs demonstrated that guanfacine is primarily metabolised via CYP3A-mediated oxidation, with subsequent phase II reactions of sulfation and glucuronidation. In pooled human hepatic microsomes, guanfacine did not inhibit the activities of the major cytochrome P450 isoenzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5) ; guanfacine is also not expected to be an inducer of CYP3A, CYP1A2 and CYP2B6. Guanfacine is a substrate of CYP3A4/3A5 and exposure is affected by CYP3A4/3A5 inducers such as rifampicin and inhibitors such as ketoconazole (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

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.

Excretion

Guanfacine elimination involves both hepatic metabolism and renal excretion via the OCT2 transporter. Following dosing with radioactively-labelled guanfacine, over 80% of the radioactivity was recovered in the urine. The major urinary radioactive components were parent drug and 3-hydroxy guanfacine glucuronide, which each comprised around 30% of the recovered radioactivity. Other urinary metabolites included guanfacine dihydrodiol and 3-hydroxy guanfacine sulfate. The elimination half-life of guanfacine is approximately 18 hours. The pharmacokinetics of guanfacine are similar in children (aged 6 to 12) and adolescent (aged 13 to 17) ADHD patients, and healthy adult volunteers.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

No carcinogenic effect was observed when mice and rats received guanfacine in their diets at doses up to 7 times the maximum recommended human dose (MHRD) of 0.12 mg/kg/day on a mg/m^2 basis for periods of 78 and 102 weeks, respectively. Exposures achieved in these studies were not measured but likely to be similar to clinical exposure at the MRHD.The negative results from genotoxicity and carcinogenicity studies suggest that guanfacine has low carcinogenic potential in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

INTUNIV modified release tablets contain the following inactive ingredients:

hypromellose, methacrylic acid - ethyl acrylate copolymer (1:1), sodium lauryl sulfate, polysorbate 80, lactose, povidone, crospovidone, colloidal anhydrous silica, microcrystalline cellulose, fumaric acid, glycerol dibehenate.

The 3 mg and 4 mg tablets also contain indigo carmine aluminium lake and iron oxide yellow.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

4 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25º C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

Blister pack

Pack size

7 or 28 tablets. Not all pack sizes may be marketed.

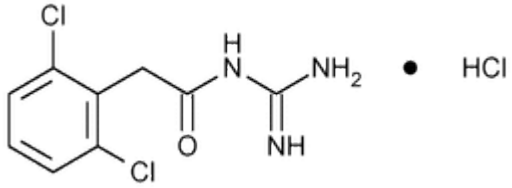
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Formula
$C_9H_9Cl_2N_3O \cdot HCl$

Chemical structure



CAS number
29110-48-3

Molecular weight
282.56

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

Shire Australia Pty Limited
Shire is now part of Takeda
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9 DATE OF FIRST APPROVAL

22 August 2017

10 DATE OF REVISION

26 September 2019.

Summary table of changes

Section Changed	Summary of new information
4.5 Transporters	Addition of text to include data from *in vitro* studies.
5.2 PHARMACOKINETIC PROPERTIES – Metabolism	Updated section to include relevant data from nonclinical studies.