

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 1 mg prolonged-release tablets
Intuniv 2 mg prolonged-release tablets
Intuniv 3 mg prolonged-release tablets
Intuniv 4 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Intuniv 1 mg tablet

Each tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine.

Intuniv 2 mg tablet

Each tablet contains guanfacine hydrochloride equivalent to 2 mg of guanfacine.

Intuniv 3 mg tablet

Each tablet contains guanfacine hydrochloride equivalent to 3 mg of guanfacine.

Intuniv 4 mg tablet

Each tablet contains guanfacine hydrochloride equivalent to 4 mg of guanfacine.

Excipient(s) with known effect

Each 1 mg tablet contains 22.41 mg of lactose (as monohydrate).

Each 2 mg tablet contains 44.82 mg of lactose (as monohydrate).

Each 3 mg tablet contains 37.81 mg of lactose (as monohydrate).

Each 4 mg tablet contains 50.42 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Intuniv 1 mg tablet

7.14mm round, white to off-white tablets debossed with '1MG' on one side and '503' on the other side.

Intuniv 2 mg tablet

12.34mm x 6.10mm oblong shaped, white to off-white tablets debossed with '2MG' on one side and "503" on the other side.

Intuniv 3 mg tablet

7.94mm round, green tablets debossed with '3MG' on one side and '503' on the other side.

Intuniv 4 mg tablet

12.34mm x 6.10mm 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 for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

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

4.2 Posology and method of administration

Treatment must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders.

Pre-treatment screening:

Prior to prescribing, it is necessary to conduct a baseline evaluation to identify patients at increased risk of somnolence and sedation, hypotension and bradycardia, QT-prolongation arrhythmia and weight increase/risk of obesity. This evaluation should address a patient's cardiovascular status including blood pressure and heart rate, documenting comprehensive history of concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see section 4.4).

Posology

Careful dose titration and monitoring is necessary at the start of treatment with Intuniv since clinical improvement and risks for several clinically significant adverse reactions (syncope, hypotension, bradycardia, somnolence and sedation) are dose- and exposure-related. Patients should be advised that somnolence and sedation can occur, particularly early in treatment or with dose increases. If somnolence and sedation are judged to be clinically concerning or persistent, a dose decrease or discontinuation should be considered.

For all patients, the recommended starting dose is 1 mg of guanfacine, taken orally once a day.

The dose may be adjusted in increments of not more than 1 mg per week. Dose should be individualised according to the patient's response and tolerability.

Depending on the patient's response and tolerability for Intuniv the recommended maintenance dose range is 0.05-0.12 mg/kg/day. The recommended dose titration for children and adolescents is provided below (see tables 1 and 2). Dose adjustments (increase or decrease) to a maximum tolerated dose within the recommended optimal weight-adjusted dose range based upon clinical judgement of response and tolerability may occur at any weekly interval after the initial dose.

Monitoring during titration

During dose titration, weekly monitoring for signs and symptoms of somnolence and sedation, hypotension and bradycardia should be performed.

Ongoing monitoring

During the first year of treatment, the patient should be assessed at least every 3 months for:

- Signs and symptoms of:
 - somnolence and sedation
 - hypotension
 - bradycardia
- weight increase/risk of obesity

It is recommended clinical judgement be exercised during this period. 6 monthly monitoring should follow thereafter, with more frequent monitoring following any dose adjustments (see section 4.4).

Table 1

Dose Titration Schedule for Children Aged 6-12 years				
Weight Group	Week 1	Week 2	Week 3	Week 4
25 kg and up Max Dose= 4 mg	1 mg	2 mg	3 mg	4 mg

Table 2

Dose Titration Schedule for Adolescents (Aged 13-17 Years)							
Weight Group ^a	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
34-41.4 kg Max Dose= 4 mg	1 mg	2 mg	3 mg	4 mg			
41.5-49.4 kg Max Dose= 5 mg	1 mg	2 mg	3 mg	4 mg	5 mg		
49.5-58.4 kg Max Dose= 6 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	
58.5 kg and above Max Dose= 7 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg ^b

^a Adolescent subjects must weigh at least 34 kg.

^b Adolescents weighing 58.5 kg and above may be titrated to a 7 mg/day dose after the subject has completed a minimum of 1 week of therapy on a 6 mg/day dose and the physician has performed a thorough review of the subject's tolerability and efficacy.

The physician who elects to use guanfacine for extended periods (over 12 months) should re-evaluate the usefulness of guanfacine every 3 months for the first year and then at least yearly based on clinical judgement (see section 4.4), and consider trial periods off medication to assess the patient's functioning without pharmacotherapy, preferably during times of school holidays.

Downward titration and discontinuation

Patients/caregivers should be instructed not to discontinue guanfacine without consulting their physician.

When stopping Intuniv, the dose must be tapered with decrements of no more than 1 mg every 3 to 7 days, and blood pressure and pulse should be monitored in order to minimise potential withdrawal effects, in particular increases in blood pressure and heart rate (see section 4.4).

In a maintenance of efficacy study, upon switching from guanfacine to placebo, 7/158 (4.4%) subjects experienced increases in blood pressure to values above 5 mmHg and also above the 95th percentile for age, sex and stature (see sections 4.8 and 5.1).

Missed dose

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 guanfacine.

Switching from other formulations of guanfacine

Immediate-release guanfacine tablets should not be substituted on a mg/mg basis, because of differing pharmacokinetic profiles.

Special populations

Adults and elderly

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

Hepatic impairment

Guanfacine is cleared both by the liver and the kidneys, and at least 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) was not assessed.

Renal impairment

Guanfacine is cleared both by the liver and the kidneys, with approximately 30% of an intact medicinal product excreted with 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) was not assessed.

Children under 6 years

Intuniv should not be used in children under the age of 6 years because efficacy and safety in this patient population has not been studied.

Patients treated with CYP3A4 and CYP3A5 inhibitors/inducers

CYP3A4/5 inhibitors have been shown to have a significant effect on the pharmacokinetics of guanfacine when co-administered. 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) (see section 4.5). In case of concomitant use of strong and moderate CYP3A inhibitors, a 50% reduction of the guanfacine dose is recommended. Due to variability in interaction effect, further dose titration may be needed (see above). If guanfacine is combined with strong enzyme inducers, a retitration to increase the dose up to a maximum daily dose 7 mg (see section 4.2), may be considered if needed. If the inducing treatment is ended, retitration to reduce the guanfacine dose is recommended during the following weeks (see section 4.5).

Method of administration

Oral use.

Intuniv 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.

Treatment is recommended only for children who are able to swallow the tablet whole without problems.

Intuniv can be administered with or without food but should not be administered with high fat meals, due to increased exposure (see section 5.2).

Intuniv should not be administered together with grapefruit juice (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypotension, bradycardia and syncope

Intuniv can cause syncope, hypotension and bradycardia. Syncope may involve risks of falls or accidents, which could result in serious harm (see sections 4.8 and 4.7).

Prior to initiation of treatment, patient's cardiovascular status including heart rate and blood pressure parameters, family history of sudden cardiac death /unexplained death, should be assessed to identify patients at increased risk of hypotension, bradycardia, and QT-prolongation/risk of arrhythmia. Monitoring of heart rate and blood pressure parameters should continue on a weekly basis during dose titration and stabilisation and at least 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.

Caution is advised when treating patients with Intuniv who have a history of hypotension, heart block, bradycardia, or cardiovascular disease, or who have a history of syncope or a condition that may predispose them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Caution is also advised when treating patients with Intuniv who are being treated concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Patients should be advised to drink plenty of fluid.

Blood pressure and heart rate increase upon discontinuation

Blood pressure and pulse may increase following discontinuation of Intuniv. In post-marketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation of Intuniv (see section 4.8). To minimise 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). Blood pressure and pulse should be monitored when reducing the dose or discontinuing Intuniv.

QTc interval

In phase II-III randomised double-blind monotherapy studies respective increases in QT_c interval prolongation that exceeded change from baseline greater than >60 ms Fridericia-correction and Bazett-correction were 0 (0.0%) and 2 (0.3%) among placebo and 1 (0.1%) and 1 (0.1%) among Intuniv patients. The clinical relevance of this finding is uncertain.

Guanfacine should be prescribed with caution in patients with a known history of QT prolongation, risk factors for torsade de pointes (e.g., heart block, bradycardia, hypokalaemia) or patients who are taking medicinal products known to prolong the QT interval. These patients should receive further cardiac evaluation based on clinical judgement (see section 4.8).

Sedation and somnolence

Intuniv may cause somnolence and sedation predominantly at the start of treatment and could typically last for 2-3 weeks and longer in some cases. It is therefore recommended that patients will be closely monitored weekly during dose titration and stabilisation (see section 4.2), and every 3 months during the first year, taking into consideration clinical judgement. Before Intuniv is used with any other centrally active depressants (such as alcohol, sedatives, phenothiazines, barbiturates, or benzodiazepines) the potential for additive sedative effects should be considered. Patients should not drink alcohol whilst taking Intuniv. Patients are advised against operating heavy equipment, driving or cycling until they know how they respond to treatment with Intuniv (see section 4.7).

Suicidal ideation

Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible change in the ADHD treatment programme.

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.

Excipients

Intuniv contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

When Intuniv is used concomitantly with CYP3A4/5 inhibitors or inducers, plasma concentrations of guanfacine may be elevated or lowered, potentially affecting the efficacy and safety of Intuniv. Intuniv can increase plasma concentrations of concomitantly administered medicinal products that are metabolised via CYP3A4/5 (see sections 4.2, 4.4 and 5.2).

Guanfacine is an *in vitro* substrate of OCT1. Potential drug interactions with drugs that inhibit OCT1 cannot be excluded.

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.

The pharmacodynamic effect of Intuniv can have an additive effect when taken with other products known to cause sedation, hypotension or QT prolongation (see section 4.4).

All drug-drug interaction studies have been performed in adults, however, the outcome is expected to be similar in the indicated paediatric age range.

QT Prolonging medicinal products

Intuniv causes a decrease in heart rate. Given the effect of Intuniv on heart rate, the concomitant use of Intuniv with QT prolonging medicinal products is generally not recommended (see section 4.4).

CYP3A4 and CYP3A5 inhibitors

Caution should be used when Intuniv is administered to patients taking ketoconazole and other moderate and strong CYP3A4/5 inhibitors, a decrease in the dose of Intuniv within the recommended dose range is proposed (see section 4.2). Co-administration of Intuniv with moderate and strong CYP3A4/5 inhibitors elevates plasma guanfacine concentrations and increases the risk of adverse reactions 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 peak plasma concentrations (C_{max}) and exposure (AUC) increased 2- and 3-fold, respectively. Other CYP3A4/5 inhibitors may have a comparable effect, see table 3 for a list of examples of moderate and strong CYP3A4/5 inhibitors, this list is not definitive.

CYP3A4 inducers

When patients are taking Intuniv concomitantly with a CYP3A4 inducer, an increase in the dose of Intuniv within the recommended dose range is proposed (see section 4.2). There was a significant decrease in the rate and extent of guanfacine exposure when co-administered with rifampin, a

CYP3A4 inducer. The peak plasma concentrations (C_{max}) and exposure (AUC) of guanfacine decreased by 54% and 70% respectively. Other CYP3A4 inducers may have a comparable effect, see table 3 for a list of examples of CYP3A4/5 inducers, this list is not definitive.

Table 3

Moderate CYP3A4/5 inhibitors	Strong CYP3A4/5 inhibitors	CYP3A4 inducers
Aprepitant	Boceprevir	Bosentan
Atazanavir	Chloramphenicol	Carbamazepine
Ciprofloxacin	Clarithromycin	Efavirenz
Crizotinib	Indinavir	Etravirine
Diltiazem	Itraconazole	Modafinil
Erythromycin	Ketoconazole	Nevirapine
Fluconazole	Posaconazole	Oxcarbazepine
Fosamprenavir	Ritonavir	Phenobarbital
Imatinib	Saquinavir	Phenytoin
Verapamil	Suboxone	Primidone
Grapefruit juice	Telaprevir	Rifabutin
	Telithromycin	Rifampicin
		St. John's Wort
<i>See section 4.2 for further dosing recommendations</i>		

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 metabolised by glucuronidation, possibly resulting in competitive inhibition. When Intuniv is co-administered with valproic acid, patients should be monitored for potential additive central nervous system (CNS) effects and consideration should be given to the monitoring of serum valproic acid concentrations. Adjustments in the dose of valproic acid and Intuniv may be indicated when co-administered.

Antihypertensive medicinal products

Caution should be used when Intuniv is administered concomitantly with antihypertensive medicinal products, due to the potential for additive pharmacodynamic effects such as hypotension and syncope.

CNS depressant medicinal products

Caution should be used when Intuniv is administered concomitantly with CNS depressant medicinal products (e.g., alcohol, sedatives, hypnotics, benzodiazepines, barbiturates, and antipsychotics) due to the potential for additive pharmacodynamic effects such as sedation and somnolence.

Oral Methylphenidate

In a drug interaction study, neither Intuniv nor Osmotic Release Oral System (OROS)-methylphenidate HCl extended-release were found to affect the pharmacokinetics of the other medicinal products 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 combination of Intuniv and lisdexamfetamine dimesylate.

Food interactions

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of guanfacine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Intuniv is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether guanfacine and its metabolites are excreted in human milk.

Available pharmacodynamic and toxicological data in animals have shown excretion of guanfacine and its metabolites in milk (see section 5.3). Therefore, a risk on the breast-fed infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue and/or abstain from Intuniv therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no or limited amount of data regarding effect on fertility from the use of guanfacine in humans.

Animal studies indicate an effect on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Intuniv can cause dizziness and somnolence. These effects occur predominantly at the start of treatment and may occur less frequently as treatment continues. Syncope has also been observed. It may have a moderate to severe influence on the ability to drive, use machines or cycling. Patients should be warned of these possible effects and be advised that if affected, they should avoid these activities (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

In the data set from controlled, doubled blinded and open-label clinical studies with Intuniv the most frequently reported adverse reactions (very common) include somnolence (40.6%), headache (27.4%), fatigue (18.1%), abdominal pain upper (12.0%), and sedation (10.2%). Serious adverse reactions commonly reported include hypotension (3.2%), weight increase (2.9%), bradycardia (1.5%) and syncope (uncommon) (0.7%). The adverse reactions somnolence and sedation occurred predominantly at the start of treatment and may typically last for 2-3 weeks and longer in some cases.

Tabulated list of adverse reactions

The following table presents all adverse reactions based on clinical trials and spontaneous reporting. All adverse reactions from post-marketing experience are *italicised*.

The following definitions apply to the frequency terminology used hereafter:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data).

Table 4. Adverse Drug Reactions Reported with Intuniv	
System/Organ Class Adverse Drug Reaction	Incidence Category
Immune system disorders	
Hypersensitivity	Uncommon
Metabolism and nutrition disorders	
Decreased appetite	Common
Psychiatric disorders	
Depression	Common
Anxiety	Common
Affect lability	Common
Insomnia	Common
Middle insomnia	Common
Nightmare	Common
Agitation	Uncommon
Hallucination	Uncommon
Nervous system disorders	
Somnolence	Very common
Headache	Very common
Sedation	Common
Dizziness	Common
Lethargy	Common
Convulsion	Uncommon
Syncope/loss of consciousness	Uncommon
Dizziness postural	Uncommon
Hypersomnia	Rare
Cardiac disorders	
Bradycardia	Common
Atrioventricular block first degree	Uncommon
<i>Tachycardia</i>	<i>Uncommon</i>
Sinus arrhythmia	Uncommon
Vascular disorders	
Hypotension	Common
Orthostatic hypotension	Common
Pallor	Uncommon
Hypertension	Rare
<i>Hypertensive encephalopathy</i>	<i>Very rare</i>
Respiratory, thoracic, and mediastinal disorders	
Asthma	Uncommon
Gastrointestinal disorders	
Abdominal pain	Very common
Vomiting	Common
Diarrhoea	Common
Nausea	Common
Constipation	Common

Table 4. Adverse Drug Reactions Reported with Intuniv	
System/Organ Class	Incidence Category
Adverse Drug Reaction	
Abdominal/stomach discomfort	Common
Dry mouth	Common
Dyspepsia	Uncommon
Skin and subcutaneous tissue disorders	
<i>Rash</i>	<i>Common</i>
<i>Pruritus</i>	<i>Uncommon</i>
Renal and urinary disorders	
Enuresis	Common
Pollakiuria	Uncommon
Reproductive system and breast disorders	
<i>Erectile dysfunction</i>	<i>Not known</i>
General disorders	
Fatigue	Very common
Irritability	Common
Asthenia	Uncommon
Chest pain	Uncommon
Malaise	Rare
Investigations	
Blood pressure decreased	Common
Weight increased	Common
Blood pressure increased	Uncommon
Heart rate decreased	Uncommon
Alanine aminotransferase increased	Uncommon

Description of selected adverse reactions

Somnolence/sedation, hypotension, bradycardia and syncope

In the overall pool of guanfacine-treated patients, somnolence occurred in 40.6% and sedation in 10.2% of guanfacine-treated patients. Bradycardia occurred in 1.5%, hypotension in 3.2% and syncope occurred in 0.7% of all guanfacine-treated patients. The occurrence of somnolence/sedation and hypotension was most prominent in the first few weeks of treatment and diminished gradually thereafter.

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

Careful follow-up for weight suggests that children and adolescents who took Intuniv in the study (i.e., treatment for 7 days per week throughout the year) have demonstrated by an age- and sex-normalised mean change from baseline in BMI percentile, 4.3 over 1 year (average percentiles at baseline and 12 months were 68.3 and 73.1, respectively). Consequently, as part of routine monitoring height, weight and BMI should be monitored at the start of treatment and every 3 months during the first year, then 6 monthly taking in to consideration clinical judgement with maintenance of a growth chart.

Thorough QT/QTc study

The effect of 2 dose levels of immediate-release guanfacine (4 mg and 8 mg) on QT interval was evaluated in a double-blind, randomised, placebo- and active-controlled, cross-over study in healthy adults. An apparent increase in mean QTc was observed for both doses. This finding has no known clinical relevance.

In phase II-III randomised double-blind monotherapy studies respective increases in QTc interval prolongation that exceeded change from baseline greater than 60 ms Fridericia-correction and Bazett-correction were 0 (0.0%) and 2 (0.3%) among placebo and 1 (0.1%) and 1 (0.1%) among Intuniv patients. The clinical relevance of this finding is uncertain.

Blood pressure and heart rate increase upon discontinuation of Intuniv

Blood pressure and pulse may increase following discontinuation of Intuniv. In post-marketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation of Intuniv (see section 4.4).

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. However, individuals may have larger increases than reflected by the mean changes. 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 (see sections 4.2 and 5.1).

Adult patients

Intuniv has not been studied in adults with ADHD.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Signs and symptoms of overdose may include hypotension, initial hypertension, bradycardia, lethargy, and respiratory depression. Haemodynamic instability has also been associated with a guanfacine overdose 3 times the recommended daily dose. 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 dialysable in clinically significant amounts (2.4%).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives, antiadrenergic agents, centrally acting ATC code: C02AC02.

Mechanism of action

Guanfacine is a selective α_{2A} -adrenergic receptor agonist in that it has 15-20 times higher affinity for this receptor subtype than for the α_{2B} or α_{2C} subtypes. Guanfacine is a non-stimulant. 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 noradrenalin transmission at the α_2 -adrenergic receptors.

Pharmacodynamic effects

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

Clinical efficacy and safety

The effects of guanfacine in the treatment of ADHD has been examined 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 years, 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.

Three hundred and thirty-seven patients aged 6-17 years were evaluated in the pivotal Phase 3 Study SPD503-316, to assess safety and efficacy of once-daily dosing (children: 1-4mg/day, adolescents: 1-7 mg/day). In this 12-week (6-12 years) or 15-week (13-17 years), randomised, double-blind, parallel-group, placebo- and active-reference (atomoxetine), dose-titration study, guanfacine showed significantly greater efficacy than placebo on symptoms of ADHD based upon investigator ratings on the ADHD Rating Scale (ADHD-RS). 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 5.

Table 5. 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) <i>Effect size</i>	Responders	Difference from placebo (95% CI)
Guanfacine	114	43.1 (5.5)	-23.9 (12.4)	-8.9 (-11.9, -5.8) <i>0.8</i>	64.3%	21.9% (9.2 ; 34.7)
Atomoxetine	112	43.7 (5.9)	-18.6 (11.9)	-3.8 (-6.8, -0.7) <i>0.3</i>	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 ($\geq 30\%$ reduction from baseline in ADHD-RS-IV Total Score and a CGI-I value of 1 or 2) was 64.3% for guanfacine, 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).

In addition a 15-week, double-blind, randomised, placebo-controlled, dose-optimisation study (SPD503-312) conducted in adolescents aged 13-17 years (n=314) to confirm the efficacy, safety, and tolerability of guanfacine (1-7 mg/day) in the treatment of ADHD. Guanfacine showed a significantly greater improvement in the ADHD-RS-IV total score compared with subjects receiving placebo. 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.

Study (SPD503-315) was a 41 week long term maintenance of efficacy study which included an open-label phase (up to 13 weeks) followed by double-blind, 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 guanfacine (children: 1-4 mg/day, adolescents: 1-7 mg/day) in the treatment of ADHD. Guanfacine 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 $\geq 50\%$ increase 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. At the end of their double-blind treatment, a significantly larger proportion of subjects in the guanfacine compared with placebo group were normal or borderline mentally ill as measured by the clinical global impression of severity (CGI-S) that includes assessment of functioning. Superiority (statistical significance) over placebo on the family and school, and learning domains of the WFIRS-P score was not consistently established in this study.

Similar results for the efficacy of guanfacine in the treatment of ADHD were 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 and SPD503-304 were 8 and 9 weeks in duration, respectively, both conducted in the United States. Guanfacine 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, $p<0.02$).

Study SPD503-314 was conducted in children aged 6-12 years to assess the efficacy of once daily dosing with guanfacine (1-4 mg) administered either in the morning or the evening. This was a double-blind, randomised, placebo-controlled, dose-optimisation study, 9-weeks in duration conducted in the United States and Canada. 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. Guanfacine 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, $p<0.001$).

Co-administration with Psychostimulants

The effect of co-administration with psychostimulants was examined in an add-on study in partial responders to psychostimulants. The study was double-blind, randomised, placebo-controlled, multi-centre, dose-optimisation 9-weeks study. It was designed to evaluate the efficacy and safety of guanfacine (1, 2, 3, and 4 mg/day) when co-administered with long-acting psychostimulants (amphetamine, lisdexamphetamine, methylphenidate, dexamethylphenidate) in children and adolescents aged 6-17 years with a diagnosis of ADHD and a suboptimal, partial response to psychostimulants. Suboptimal response was defined as an ADHD-RS-IV total score of ≥ 24 and a CGI-S score ≥ 3 at screening and baseline. The primary efficacy assessment was the ADHD-RS-IV total score. The results showed that patients treated with add-on guanfacine improved more on the ADHD-RS-IV compared to those treated with add-on placebo (20.7 (12.6) points vs. 15.9 (11.8); difference: 4.9 95% CI 2.6, 7.2). No age differences were observed with respect to response to the ADHD-RS-IV.

ADHD with Oppositional Symptoms Study

Study SPD503-307 was a 9-week, double-blind, randomised, placebo-controlled, dose-optimisation study with guanfacine (1-4 mg/day) conducted in children aged 6-12 years with ADHD and oppositional symptoms ($n=217$). 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. Results show statistically significantly ($p\leq 0.05$) 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.

5.2 Pharmacokinetic properties

Absorption

Guanfacine is readily absorbed, with peak plasma concentrations reached approximately 5 hours after oral administration in paediatric patients (children and adolescents 6-17 years old inclusive). In adults, the mean exposure of guanfacine increased (C_{\max} ~75% and AUC ~40%) when Intuniv was taken together with a high fat meal, compared to intake in the fasted state (see section 4.2).

Distribution

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

Biotransformation

Guanfacine is metabolised via CYP3A4/5-mediated oxidation, with subsequent phase II reactions of sulphation and glucuronidation. The major circulating metabolite is 3-OH-guanfacine sulphate which lacks pharmacological activity.

Guanfacine is a substrate of CYP3A4 and CYP3A5, and exposure is affected by CYP3A4 and CYP3A5 inducers and inhibitors. In human hepatic microsomes, guanfacine did not inhibit the activities of the other 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.

Transporters

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

Elimination

Guanfacine is cleared by the kidneys via filtration and active secretion and the liver. Active renal secretion is mediated via OCT2 transporter. Renal excretion is the major elimination pathway (80%) with parent drug accounting for 30% of the urinary radioactivity. The major urinary metabolites were 3-hydroxy guanfacine glucuronide, guanfacine dihydrodiol, 3-hydroxy guanfacine sulphate. The elimination half-life of guanfacine is approximately 18 hours.

The pharmacokinetics of guanfacine is similar in children (aged 6 to 12) and adolescents (aged 13 to 17) ADHD patients, and healthy adult volunteers.

Special populations

There have been no studies performed in children with ADHD under the age of 6 years with Intuniv.

Systemic exposure to guanfacine is similar for men and women given the same mg/kg dose.

Formal pharmacokinetic studies for race have not been conducted. There is no evidence of any impact of ethnicity on the pharmacokinetics of Intuniv.

5.3 Preclinical safety data

No carcinogenic effect of guanfacine was observed in studies of 78 weeks in mice at doses up to 10 mg/kg/day. A significant increase in incidence of adenomas of the pancreatic islet was observed in male rats treated with 5 mg/kg/day guanfacine for 102 weeks but not in female rats. The clinical relevance is unknown.

Guanfacine was not genotoxic in a variety of test models, including the Ames test and an *in vitro* chromosomal aberration test.

General toxicity observed in animals (rat, dog) upon treatment with guanfacine included prolongation of uncorrected QT interval (heart), atrophic spleen and decreased white blood cells, affected liver – increased bilirubin and ALT levels included, irritated and inflamed intestines, increased creatinine and blood urea nitrogen levels (kidney), corneal clouding (eye) in rat and mouse only, alveolar macrophage infiltration & pneumonitis and reduced spermatogenesis.

No adverse effects were observed in a fertility study in female rats at doses up to 22 times the maximum recommended human dose on a mg/m² basis.

Male fertility was affected at 8 mg/kg/day, the lowest dose tested, equivalent of 10.8 times the maximum recommended human dose of 0.12 mg/kg on a mg/m² basis. Due to lack of proper toxicokinetic data, comparison to human clinical exposure was not possible.

Guanfacine showed embryo foetal developmental toxicity in mice and rats (NOAEL 0.5 mg/kg/day) and in rabbits (NOAEL 3.0 mg/kg/day) in the presence of maternal toxicity. Due to a lack of proper toxicokinetic data, comparison to human clinical exposure was not possible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose 2208
Methacrylic acid-Ethyl acrylate copolymer
Lactose monohydrate
Povidone
Crospovidone Type A
Microcrystalline cellulose
Silica, colloidal anhydrous
Sodium laurilsulphate
Polysorbate 80
Fumaric acid
Glycerol dibehenate

In addition 3 mg and 4 mg tablets include

Indigo carmine aluminium lake E 132
Iron oxide yellow E 172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The blister strips comprise of 2 layers, a clear thermoformable rigid film which is laminated with PCTFE to a PVC backing to which a push-through aluminium foil is adhered. The blisters are contained in cardboard cartons.

Intuniv 1 mg pack sizes: 7 or 28 tablets.
Intuniv 2 mg pack sizes: 7, 28 or 84 tablets.
Intuniv 3 mg pack sizes: 28 or 84 tablets.
Intuniv 4 mg pack sizes: 28 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
5 Riverwalk,
Citywest Business Campus,
Dublin 24,
IRELAND

8. MARKETING AUTHORISATION NUMBER(S)

Intuniv 1 mg tablet
EU/1/15/1040/001-002

Intuniv 2 mg tablet
EU/1/15/1040/003-005

Intuniv 3 mg tablet
EU/1/15/1040/006-007

Intuniv 4 mg tablet
EU/1/15/1040/008-009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17/09/2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

SHIRE PHARMACEUTICALS LIMITED
Hampshire International Business Park
Chineham
Basingstoke
Hampshire
RG24 8EP
UNITED KINGDOM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

1. Prior to launch of Intuniv in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media,

distribution modalities, and any other aspects of the programme, with the National Competent Authority.

2. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Intuniv is launched all healthcare professionals who are expected to prescribe Intuniv are informed through an information letter on having access to / are provided with the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet
- Educational material (including prescriber checklist) for the healthcare professionals

The Educational material and Prescriber checklist shall contain the following key messages:

- Information on the risks associated with Intuniv: Bradycardia, Syncope, Hypotension/decreased blood pressure, withdrawal blood pressure increase, sedative events and weight increase
 - Checklist prior to initiating treatment with Intuniv to identify patients at risk for serious undesirable effects
 - Checklist for ongoing monitoring and safety management of patients including titration phase during treatment with Intuniv
 - Chart for ongoing monitoring (vital signs, height, weight) of patients during treatment with Intuniv.
 - Checklist for discontinuation of guanfacine including monitoring blood pressure and pulse of patients during downward titration.
- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
SHP503-401: In order to investigate the long term safety (especially effects on neurocognitive function) of Intuniv in Children and Adolescents Aged 6-17 Years with ADHD, the MAH should conduct and submit the results of a comparative safety study according to an agreed protocol.	Submission of final study Report: 31-January-2022

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 1 mg prolonged-release tablets
Guanfacine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 prolonged-release tablets
28 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.
Swallow the tablet whole. Do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1040/001 7 prolonged-release tablets
EU/1/15/1040/002 28 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Intuniv 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 1 mg prolonged-release tablets

Guanfacine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited (as MA Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 2 mg prolonged-release tablets
Guanfacine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains guanfacine hydrochloride equivalent to 2 mg of guanfacine.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 prolonged-release tablets
28 prolonged-release tablets
84 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.
Swallow the tablet whole. Do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1040/003 7 prolonged-release tablets
EU/1/15/1040/004 28 prolonged-release tablets
EU/1/15/1040/005 84 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Intuniv 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 2 mg prolonged-release tablets

Guanfacine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited (as MA Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 3 mg prolonged-release tablets
Guanfacine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains guanfacine hydrochloride equivalent to 3 mg of guanfacine.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets
84 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.
Swallow the tablet whole. Do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1040/006 28 prolonged-release tablets
EU/1/15/1040/007 84 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Intuniv 3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 3 mg prolonged-release tablets

Guanfacine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited (as MA Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 4 mg prolonged-release tablets
Guanfacine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains guanfacine hydrochloride equivalent to 4 mg of guanfacine.

3. LIST OF EXCIPIENTS

Also contains lactose, See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets
84 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.
Swallow the tablet whole. Do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1040/008 28 prolonged-release tablets
EU/1/15/1040/009 84 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Intuniv 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Intuniv 4 mg prolonged-release tablets

Guanfacine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceuticals Ireland Limited (as MA Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Intuniv 1mg prolonged-release tablets

Intuniv 2mg prolonged-release tablets

Intuniv 3mg prolonged-release tablets

Intuniv 4mg prolonged-release tablets

Guanfacine

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace “you” with “your child” throughout.

What is in this leaflet:

1. What Intuniv is and what it is used for
2. What you need to know before you take Intuniv
3. How to take Intuniv
4. Possible side effects
5. How to store Intuniv
6. Contents of the pack and other information

1. What Intuniv is and what it is used for

What Intuniv is

Intuniv contains the active substance guanfacine. This medicine belongs to a group of medicines which affects brain activity. This medicine can help improve your attention, concentration and make you less impulsive and hyperactive.

What Intuniv is used for

This medicine is used to treat ‘attention deficit hyperactivity disorder’ (ADHD) in children and adolescents 6-17 years old for whom current stimulant medication is not appropriate and/or current medication does not adequately control ADHD symptoms.

The medicine is given as part of a treatment programme, which usually includes the following:

- psychological therapy
- educational therapy
- social therapy

You should talk to your doctor if you do not feel better or if you feel worse and very sleepy or drowsy after taking this medicine for around 6 weeks. Your doctor may want to review your treatment.

About ADHD

People with ADHD find it hard to:

- sit still
- concentrate.

ADHD can cause problems with everyday life. Children and young people with ADHD may have difficulty learning and doing homework. They can find it hard to behave well at home, at school or in other places.

ADHD does not affect the intelligence of a child or young person.

2. What you need to know before you take Intuniv

Do not take Intuniv if:

- you are allergic to guanfacine or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking this medicine if:

- you have low or high blood pressure, heart problems or have a family history of heart problems
- you have fainted recently
- you have thoughts or feelings of suicide
- you suffer from any other psychiatric conditions

Intuniv may affect your weight and height if taking for long periods, your doctor will therefore monitor your growth.

Do not stop taking Intuniv without talking to your doctor. If you suddenly stop taking Intuniv, you may develop withdrawal symptoms of increased heart rate and high blood pressure (see section 4).

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking this medicine. This is because this medicine can make these problems worse. Your doctor will routinely monitor you to see how this medicine affects you.

Children (under 6 years old) and adults (18 years and over)

This medicine should not be used in children under 6 years of age and adults 18 years and over because it is not known if it works or is safe.

Checks your doctor will do when you take Intuniv

Before you start taking this medicine your doctor will check to make sure this medicine is safe for you and that it will help you. While you are taking this medicine your doctor will repeat these checks weekly during initial dosing, after dose adjustments, at least every 3 months for the first year and then at least twice a year. These checks may include:

- your blood pressure and heart rate and other checks on your heart if appropriate
- your response to treatment, in particular if it makes you sleepy or drowsy
- your height and weight

Other medicines and Intuniv

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Intuniv and some other medicines can affect each other.

In particular, tell your doctor or pharmacist if you are taking any of the following types of medicines:

- medicines that lower your blood pressure (antihypertensives)
- medicines for epilepsy such as valproic acid
- medicines that make you sleepy (sedatives)
- medicines for mental health problems (benzodiazepines, barbiturates and antipsychotics)
- medicines that can affect the way Intuniv is eliminated by the liver (please see table below)

Medicines	Used to treat
Aprepitant	Nausea and vertigo.
Atazanavir, efavirenz, etravirine, fosamprenavir, indinavir, nevirapine, ritonavir, saquinavir	HIV infection.
Ciprofloxacin, chloramphenicol, clarithromycin, erythromycin, rifabutin, rifampicin, telithromycin	Bacterial infections.
Fluconazole, itraconazole, posaconazole	Fungal infections.
Crizotinib, imatinib	Cancer.
Diltiazem, verapamil	Cardiovascular conditions.
Boceprevir, telaprevir	Viral hepatitis.
Suboxone	Substance dependence.
Bosentan	Cardiovascular conditions (e.g. constriction of blood vessels in the lung).
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone	Used to control epilepsy.
Modafinil	Is a medicine that promotes alertness and is used to treat sleep disorders.
St. John's Wort	Is a herbal preparation that is used to treat depression.

If any of the above apply to you or you are not sure, talk to your doctor or pharmacist before taking this medicine.

Intuniv with food, drinks and alcohol

- Do not take this medicine with fatty foods (e.g., high fat breakfast), as it may affect the way this medicine works.
- Do not take grapefruit juice with this medicine as it can have an effect on the way this medicine works.
- Do not drink alcohol when taking this medicine as it may make you sleepy or drowsy.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- Do not take this medicine if you are pregnant or you are not using contraception. It is not known if Intuniv will affect your unborn baby.
- Do not breast-feed while taking Intuniv unless told to do so by your doctor.

Driving and using machines

You may feel dizzy and drowsy when taking this medicine, especially at the start of treatment and this may last for 2 to 3 weeks possibly longer. If this happens do not drive, cycle, use any tools or machines or participate in activities that could cause injury until you know how this medicine affects you. Fainting has also been reported but is not a common effect.

Intuniv contains lactose:

Lactose is a type of sugar. If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor or pharmacist before taking this medicine.

3. How to take Intuniv

Your treatment will start under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders.

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

As part of your treatment your doctor will closely monitor how Intuniv is affecting you during initial dosing and/or dose adjustments.

How much to take

- Your doctor will start you on 1 mg per day. Your doctor may increase your dose based on your body weight and how Intuniv is working for you but not by more than 1 mg per week. Depending on how you respond to treatment your doctor may increase your dose more slowly. The recommended dose is between 0.05 up to 0.12 mg per kg of bodyweight per day.
- You may not notice an immediate effect upon starting treatment, some patients may notice an improvement after the first week but it could take longer.
- Your daily dose will be between 1 and 7 mg depending on your age and how you respond to Intuniv, but not more than 7 mg.

How to take Intuniv

- This medicine should be taken once a day either in the morning or evening.
- It can be taken with or without food, but do not take it with fatty foods (e.g., high fat breakfast).
- Swallow the tablet whole with a drink of water or other liquid (but not grapefruit juice).
- Do not break, crush or chew the tablet; this will affect how the tablet works. Tell your doctor if you cannot swallow the tablet whole.

Length of treatment

If you need to take Intuniv for more than a year your doctor will monitor your response to treatment and your doctor may stop the medicine for a short time; this may happen during a school holiday. This will show if you still need to take the medicine.

If you take more Intuniv than you should

If you take more Intuniv than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you and tell them how much you have taken.

The following effects may happen: low or high blood pressure, slow heart rate, slow breathing rate, feeling tired or exhausted.

If you forget to take Intuniv

If you forget a dose, wait until the next day and take your usual dose.

- If you have missed two or more doses talk to your doctor as you may need to restart Intuniv with a lower dose.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Intuniv

Do not stop taking this medicine without first talking to your doctor.

- If you stop taking this medicine your blood pressure and heart rate may increase (see section 4 below).
- To stop the medicine, your doctor will slowly reduce your Intuniv dose to minimise any side effects.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you are worried, speak to your doctor.

If you feel unwell in any way while you are taking your medicine please tell an adult straight away.

Serious side effects

The following serious side effects have been reported. Common: feeling drowsy (sedation), feeling dizzy (hypotension), slow heart beat (bradycardia). Uncommon: feeling faint or loss of consciousness (syncope). Very rare: a serious withdrawal side effect of high blood pressure after suddenly stopping Intuniv; symptoms may include headaches, feeling confused, nervousness, agitation, and tremors (hypertensive encephalopathy).

Some of these side effects are more likely to occur at the start of treatment and may disappear as you continue with your treatment, if you experience any of these side effects contact your doctor straight away.

Very common: may affect more than 1 in 10 people

- feeling sleepy (somnolence)
- feeling tired (fatigue)
- headache
- tummy pain (abdominal pain).

Common: may affect up to 1 in 10 people

- feeling restless or irritable
- trouble sleeping (insomnia) or broken sleep (middle insomnia) or nightmares
- feeling depressed, worried (anxiety) or having mood swings (affect lability)
- lack of energy (lethargy)
- weight gain
- loss of appetite
- have a dry mouth
- wetting yourself (enuresis)
- feeling (nausea) or being sick (vomiting)
- diarrhoea, abdominal discomfort or constipation
- low blood pressure when standing up (orthostatic hypotension)
- rash.

Uncommon: may affect up to 1 in 100 people

- allergic reaction (hypersensitivity)
- chest pain
- indigestion (dyspepsia)

- trouble breathing (asthma)
- feeling weak (asthenia)
- pale skin colour (pallor)
- fits or convulsions
- need to urinate frequently (pollakiuria)
- feeling agitated
- changes in liver blood test results (increased alanine aminotransferase)
- increase in blood pressure
- unusual heart rhythm (sinus arrhythmia and first-degree arterioventricular block)
- fast heart beat (tachycardia)
- reduced heart rate
- feeling dizzy when standing up (postural dizziness)
- itchy skin (pruritus)
- seeing or hearing things that are not there (hallucination).

Rare: may affect up to 1 in 1,000 people

- sleeping more than normal (hypersomnia)
- high blood pressure (hypertension)
- feeling unwell (malaise).

Very rare: may affect up to 1 in 10,000 people

- a serious withdrawal side effect of high blood pressure after suddenly stopping Intuniv; symptoms may include headaches, feeling confused, nervousness, agitation, and tremors (hypertensive encephalopathy).

Not known: frequency cannot be estimated from the available data

- difficulty to get or keep an erection (erectile dysfunction).

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Intuniv

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister pack after EXP.

The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not use this medicine if the tablets or blister pack look damaged.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Intuniv contains

- Each 1 mg tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine
- Each 2 mg tablet contains guanfacine hydrochloride equivalent to 2 mg of guanfacine
- Each 3 mg tablet contains guanfacine hydrochloride equivalent to 3 mg of guanfacine
- Each 4 mg tablet contains guanfacine hydrochloride equivalent to 4 mg of guanfacine

- The other ingredients are hypromellose, methacrylic acid-ethyl acrylate copolymer, lactose monohydrate, povidone, crospovidone (Type A), microcrystalline cellulose, silica colloidal anhydrous, sodium laurilsulphate, polysorbate 80, fumaric acid, glyceryl dibehenate.
- The 3 mg and 4 mg tablets also contain indigo carmine E 132 and yellow iron oxide E 172

What Intuniv looks like and contents of the pack

Intuniv is a prolonged-release tablet which means that the active substance is released from the tablet over a period of time. The tablets come in pack sizes of 7, 28 or 84 but not all pack sizes may be available.

- The 1 mg prolonged-release tablets are round and white, hard tablets, debossed with 1MG on one side and 503 on the other side.
- The 2 mg prolonged-release tablets are oval and white, hard tablets, debossed with 2MG on one side and 503 on the other side.
- The 3 mg prolonged-release tablets are round and green, hard tablets, debossed with 3MG on one side and 503 on the other side.
- The 4 mg prolonged-release tablets are oval and green, hard tablets, debossed with 4MG on one side and 503 on the other side.

Marketing Authorisation Holder

Shire Pharmaceuticals Ireland Limited
5 Riverwalk
Citywest Business Campus
Dublin 24
Ireland
Tel + 44 (0) 800 055 6614
e-mail medinfouk@shire.com

Manufacturer

Shire Pharmaceuticals Limited
Hampshire International Business Park
Basingstoke
Hampshire RG24 8EP
UK
Tel +44 (0)800-055 6614
e-mail medinfouk@shire.com

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

ANNEX IV

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS
OF THE MARKETING AUTHORISATION(S)**

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for guanfacine, the scientific conclusions of CHMP are as follows:

One serious case of erectile dysfunction, which occurred in the context of a dose upward titration pointing toward a biological gradient or dose response relationship, was reported during the period covered by this Periodic Safety Update Report (PSUR). There is a positive temporal relationship in the development of the Adverse Drug Reaction (ADR) 'erectile dysfunction' and worsening of pruritus and rash pruritic events with a short time to onset (1 day) after the dose increase and these events were resolved after the drug was withdrawn, indicating positive dechallenge. The concomitant medication melatonin is labelled for rash and rash pruritic but not for erectile dysfunction. No other potential confounding factors have been described. The information contained in this single case suggests a positive association between guanfacine and development of erectile dysfunction, which is also supported by the biological plausibility: the nor-adrenergic system is important in controlling male sexual function, from the Central Nervous System through stimulation of those areas regulating penile erection. Male sexual behaviour was suppressed in rats given alpha2-adrenoceptors agonist clonidine by direct injection into the medial preoptic area.

There is also evidence for a direct adrenergic regulation of penile veins, the predominant effect occurs through the alpha1-adrenoceptors but there remains the potential involvement of alpha2-adrenoceptors. Stimulation of the alpha2-adrenoceptors in the cavernosal smooth muscle is known to be involved in erectile dysfunction.

Based on the available evidence, the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that erectile dysfunction should be added to section 4.8 of the SmPC under the SOC 'Reproductive system and breast disorders' with a 'not known' frequency with consequential update to section 4 of the Package Leaflet.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing guanfacine were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for guanfacine the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing guanfacine is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.