ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paxneury 1 mg prolonged-release tablets
Paxneury 2 mg prolonged-release tablets
Paxneury 3 mg prolonged-release tablets
Paxneury 4 mg prolonged-release tablets
Paxneury 5 mg prolonged-release tablets
Paxneury 6 mg prolonged-release tablets
Paxneury 7 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Paxneury 1 mg prolonged-release tablet
Each tablet contains guanfacine hydrochloride equivalent to 1 mg of guanfacine.
Excipient(s) with known effect: Each tablet contains 41.32 mg of lactose (as monohydrate).

Paxneury 2 mg prolonged-release tablet
Each tablet contains guanfacine hydrochloride equivalent to 2 mg of guanfacine.
Excipient(s) with known effect: Each tablet contains 82.63 mg of lactose (as monohydrate).

Paxneury 3 mg prolonged-release tablet
Each tablet contains guanfacine hydrochloride equivalent to 3 mg of guanfacine.
Excipient(s) with known effect: Each tablet contains 17.56 mg of lactose (as monohydrate).

Paxneury 4 mg prolonged-release tablet
Each tablet contains guanfacine hydrochloride equivalent to 4 mg of guanfacine.
Excipient(s) with known effect: Each 4 mg tablet contains 23.41 mg of lactose (as monohydrate).

Paxneury 5 mg prolonged-release tablet
Each tablet contains guanfacine hydrochloride equivalent to 5 mg of guanfacine.
Excipient(s) with known effect: Each 5 mg tablet contains 29.26 mg of lactose (as monohydrate).

Paxneury 6 mg prolonged-release tablet
Each tablet contains guanfacine hydrochloride equivalent to 6 mg of guanfacine.
Excipient(s) with known effect: Each 6 mg tablet contains 35.11 mg of lactose (as monohydrate).

Paxneury 7 mg prolonged-release tablet
Each tablet contains guanfacine hydrochloride equivalent to 7 mg of guanfacine.
Excipient(s) with known effect: Each 7 mg tablet contains 40.96 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets

Paxneury 1 mg prolonged-release tablet
Guanfacine 1 mg prolonged-release tablets are white, 8 mm diameter round, biconvex tablets with the inscription “1” on one side.

Paxneury 2 mg prolonged-release tablet

Guanfacine 2 mg prolonged-release tablets are white, 14 x 6 mm oblong, biconvex tablets with the inscription “II” on one side.

Paxneury 3 mg prolonged-release tablet
Guanfacine 3 mg prolonged-release tablets are white, 6 mm diameter round, biconvex tablets with the inscription “3” on one side.

Paxneury 4 mg prolonged-release tablet
Guanfacine 4 mg prolonged-release tablets are white, 7 mm diameter round, biconvex tablets with the inscription “IV” on one side.

Paxneury 5 mg prolonged-release tablet
Guanfacine 5 mg prolonged-release tablets are white, 8 mm diameter round, biconvex tablets with the inscription “V” on one side.

Paxneury 6 mg prolonged-release tablet
Guanfacine 6 mg prolonged-release tablets are white, 9 mm diameter round, biconvex tablets with the inscription “VI” on one side.

Paxneury 7 mg prolonged-release tablet
Guanfacine 7 mg prolonged-release tablets are white, 12.5 x 6.5 mm oblong, biconvex tablets with the inscription “7” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paxneury 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.

Paxneury 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 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 Paxneury 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 treatment, 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
If a dose is missed, the prescribed dose 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. Therefore, guanfacine should not be used in this group.

Hepatic impairment
Dose reduction may be required in patients with different degrees of hepatic impairment (see section 5.2).
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
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 (see section 5.2).

Children under 6 years
The safety and efficacy of guanfacine in children aged less than 6 years have not yet been established. No data are available.

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 of 7 mg may be considered if needed. If the inducing treatment is ended, retitration to reduce the guanfacine dose is recommended during the following weeks (see section 4.5).

Method of administration

Oral use.

Guanfacine is taken once daily either morning or evening. Tablets 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.

Guanfacine can be administered with or without food but should not be administered with high fat meals, due to increased exposure (see sections 4.5 and 5.2).

Guanfacine 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

Guanfacine 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 guanfacine 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 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 (see section 4.5). 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 guanfacine. In post-marketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation of treatment (see section 4.8). To minimise the risk of an increase in blood pressure upon discontinuation, the total daily dose 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 treatment.

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 guanfacine 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 (see section 4.5). These patients should receive further cardiac evaluation based on clinical judgement (see section 4.8).

Sedation and somnolence

Guanfacine 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 guanfacine 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 (see section 4.5).
Patients should not drink alcohol whilst taking guanfacine.

Patients are advised against operating heavy equipment, driving or cycling until they know how they respond to treatment with guanfacine (see section 4.7).

Suicidal ideation

There have been post-marketing reports of suicide-related events (including suicidal ideation, attempts and completed suicide) in patients treated with guanfacine. In most cases, patients had underlying psychiatric disorders. Therefore, it is recommended that caregivers and physicians monitor patients for signs of suicide-related events, including at dose initiation/optimisation and drug discontinuation. Patients and caregivers should be encouraged to report any distressing thoughts or feelings at any time to their healthcare professional.

Aggression

Aggressive behaviour or hostility has been reported in clinical trials and in the post-marketing experience of guanfacine. Patients treated with guanfacine should be monitored for the appearance of aggressive behaviour or hostility.

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

Children and adolescents treated with guanfacine 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

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

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium- free’.

4.5 Interaction with other medicinal products and other forms of interaction

When guanfacine 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 guanfacine. Guanfacine 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* 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 guanfacine can have an additive effect when taken with other products known to cause sedation, hypotension or QT prolongation (see section 4.4).

Interaction studies have only been performed in adults. However, the outcome is expected to be similar in the indicated paediatric age range.

QT prolonging medicinal products

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

CYP3A4 and CYP3A5 inhibitors

Caution should be used when guanfacine is administered to patients taking ketoconazole and other moderate and strong CYP3A4/5 inhibitors, a decrease in the dose of guanfacine within the recommended dose range is proposed (see section 4.2). Co-administration of guanfacine 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 guanfacine concomitantly with a CYP3A4 inducer, an increase in the dose of guanfacine 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 rifampicin, 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	Nevirapine
Fluconazole	Posaconazole	Oxcarbazepine
Fosamprenavir	Ritonavir	Phenobarbital
Imatinib	Saquinavir	Phenytoin

Verapamil	Suboxone	Primidone
Grapefruit juice	Telaprevir	Rifabutin
	Telithromycin	Rifampicin
		St. John's wort
See section 4.2 for further dosing recommendations		

Valproic acid

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

Antihypertensive medicinal products

Caution should be used when guanfacine is administered concomitantly with antihypertensive medicinal products, due to the potential for additive pharmacodynamic effects such as hypotension and syncope (see section 4.4).

CNS depressant medicinal products

Caution should be used when guanfacine 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 (see section 4.4).

Oral methylphenidate

In an interaction study, neither guanfacine 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 guanfacine 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 guanfacine and lisdexamfetamine dimesylate.

Food interactions

Guanfacine 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 (see section 4.2).

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).
Guanfacine 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 guanfacine 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

Guanfacine may have a moderate to severe influence on the ability to drive and use machines. Guanfacine 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. 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

The most frequently reported adverse reactions include somnolence (40.6 %), headache (27.4 %), fatigue (18.1 %), abdominal pain upper (12.0 %), and sedation (10.2 %). The most serious adverse reactions commonly reported include hypotension (3.2 %), weight increase (2.9 %), bradycardia (1.5 %) and syncope (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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 4. Adverse reactions

System/Organ class	Adverse 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 Agitation Aggression Hallucination	Common Uncommon Uncommon Uncommon
Nervous system disorders	Somnolence Headache Sedation Dizziness Lethargy Convulsion Syncope/loss of consciousness Postural dizziness Hypersomnia	Very common Very common Common Common Common Uncommon Uncommon Uncommon Rare
Cardiac disorders	Bradycardia Atrioventricular block first degree *Tachycardia* Sinus arrhythmia	Common Uncommon *Uncommon* Uncommon
Vascular disorders	Hypotension Orthostatic hypotension Pallor Hypertension *Hypertensive encephalopathy*	Common Common Uncommon Rare *Very rare*
Respiratory, thoracic, and mediastinal disorders	Asthma	Uncommon
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Constipation Abdominal/stomach discomfort Dry mouth Dyspepsia	Very common Common Common Common Common Common Common Uncommon
Skin and subcutaneous tissue disorders	*Rash* *Pruritus*	*Common* *Uncommon*
Renal and urinary disorders	Enuresis Pollakiuria	Common Uncommon
Reproductive system and breast disorders	*Erectile dysfunction*	*Not known*
General disorders and administration site conditions	Fatigue Irritability Asthenia Chest pain Malaise	Very common Common Uncommon Uncommon Rare
Investigations	Blood pressure decreased Weight increased Blood pressure increased Heart rate decreased Alanine aminotransferase increased	Common Common Uncommon Uncommon 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 guanfacine 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 into 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 guanfacine patients. The clinical relevance of this finding is uncertain.

Blood pressure and heart rate increase upon discontinuation of guanfacine
Blood pressure and pulse may increase following discontinuation of guanfacine. In post-marketing experience, hypertensive encephalopathy has been very rarely reported upon abrupt discontinuation of guanfacine (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 guanfacine. 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

Guanfacine 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 guanfacine 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 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 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 alpha$_{2A}$-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 aged6 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 0.05-0.12 mg/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:1-4 mg/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)** ***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 % 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 guanfacine, and 64.9 % for placebo, p=0.006). Treatment failure was defined as a ≥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, lisdexamfetamine, methylphenidate, dexmethylphenidate) 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 guanfacine 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 active substance concentration.

Biotransformation

Guanfacine is metabolised via CYP3A4/5-mediated oxidation, with subsequent phase II reactions of sulfation and glucuronidation. The major circulating metabolite is 3-OH-guanfacine sulfate 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. At least 50 % of the clearance of guanfacine is hepatic. Renal excretion is the major elimination pathway (80 %) with parent active substance accounting for 30 % of the urinary radioactivity. The major urinary metabolites were 3-hydroxy guanfacine glucuronide, guanfacine dihydrodiol, 3-hydroxy guanfacine sulfate. 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 guanfacine.

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 guanfacine.

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/m^2 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/m^2 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)
Microcrystalline cellulose
Silica, colloidal anhydrous

Lactose monohydrate
Povidone K30
Crospovidone (Type A)
Methacrylic acid-ethyl acrylate copolymer (Type A)
Sodium laurilsulfate
Polysorbate 80
Fumaric acid
Glycerol dibehenate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC / Aluminium blister

Paxneury 1 mg prolonged-release tablet: Pack size of 14 or 28 tablets.

Paxneury 2 mg prolonged-release tablet: Pack size of 14 or 28 tablets.

Paxneury 3 mg prolonged-release tablet: Pack size of 28 tablets.

Paxneury 4 mg prolonged-release tablet: Pack size of 28 tablets.

Paxneury 5 mg prolonged-release tablet: Pack size of 28 tablets.

Paxneury 6 mg prolonged-release tablet: Pack size of 28 tablets.

Paxneury 7 mg prolonged-release tablet: Pack size of 28 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

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona, 69
08970 Sant Joan Despí
Barcelona, Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1908/001 (1 mg x 28 Prolonged-release tablets)
EU/1/24/1908/002 (2 mg x 28 Prolonged-release tablets)
EU/1/24/1908/003 (3 mg x 28 Prolonged-release tablets)
EU/1/24/1908/004 (4 mg x 28 Prolonged-release tablets)
EU/1/24/1908/005 (5 mg x 28 Prolonged-release tablets)
EU/1/24/1908/006 (6 mg x 28 Prolonged-release tablets)
EU/1/24/1908/007 (7 mg x 28 Prolonged-release tablets)
EU/1/24/1908/008 (1 mg x 14 Prolonged-release tablets)
EU/1/24/1908/009 (2 mg x 14 Prolonged-release tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 February 2025

10. DATE OF REVISION OF THE TEXT

09/2026

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