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EU RISK MANAGEMENT PLAN (RMP)

for

INTUNIV (guanfacine)

RMP Version number: 4.1

Date: 09-May-2024

[redacted]

[redacted]

EU Risk Management Plan for INTUNIV (guanfacine)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 4.1

Data lock point for this RMP: 17-March-2023

Date of final sign off: 09-May-2024

Rationale for submitting an updated RMP: The Risk Management Plan (RMP) is being updated based on Pharmacovigilance Risk Assessment Committee (PRAC) assessment report (Procedure No. EMEA/H/C/003759/II/0033/G) to remove the additional risk minimisation measures (aRMMs) and important identified risks associated with Intuniv.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable
• **Module SII Non-clinical part of the safety specification**	Table of "safety concerns from non-clinical studies" removed from this section.
• **Module SIII Clinical trial exposure**	Not applicable
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Not applicable
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	The below mentioned important identified risks have been removed based on PRAC assessment report: • Bradycardia • Syncope • Hypotension/decreased blood pressure • Withdrawal blood pressure increase • Sedative events • Weight increase
• **Module SVIII Summary of the safety concerns**	The below mentioned important identified risks have been removed based on PRAC assessment report: • Bradycardia • Syncope • Hypotension/decreased blood pressure • Withdrawal blood pressure increase • Sedative events • Weight increase

[redacted]

[redacted]

RMP Module:	Significant Changes:
Part III Pharmacovigilance plan	SPD503-401 study details and milestones updated in line with protocol amendment 7.
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Additional risk minimisation measures removed from Part V.2
Part VI Summary of the risk management plan	Important identified risks and aRMMs deleted.
Part VII Annexes	Annex 2: SPD503-401 study details and milestones updated as per part III updates. Annex 3: reference to protocol (eCTD Module) added for study SPD503-401. Annex 6: aRMMs removed as per Part V updates.

Other RMP versions under evaluation:

RMP Version number: 4.0

Submitted on: 12-July-2023

Procedure number: EMA/H/C/003759/II/0033/G

Details of the currently approved RMP:

Version number: 3.3

Approved with procedure: EMEA/H/C/003759/IB/0031

Date of approval (opinion date): 03-October-2022

QPPV name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by [redacted] Deputy EUQPPV, [redacted] on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: [redacted]

[redacted]

[redacted]

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[redacted]

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[redacted]

[redacted]

List of Abbreviations

Abbreviation	Definition/Description
ADR	Adverse Drug Reaction
ATC code	Anatomical Therapeutic Chemical classification system
BCRP	Breast Cancer Resistance Protein
BMI	Body Mass Index
BSEP	Bile Salt Export Pump
CACO-2	colorectal Adenocarcinoma Cells
C2BBe1	CACO-2 Brush Border Expressing Cell
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Peak Plasma Concentration
CNS	Central Nervous System
CYP	Cytochrome P450
DDD	Defined Daily Dose
DLP	Data Lock Point
ECG	Electrocardiogram
eCTD	electronic Common Technical Document
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GSS	Global Safety System
GVP	Good Pharmacovigilance Practice
GXR	Guanfacine Hydrochloride Prolonged Release Tablets
HEK	Human Embryonic Kidney
hERG	Human Ether- à-go-go- Related Gene
IC_{50}	Half Maximal Inhibitory Concentration
INN	International Non-proprietary Names
LQTS	Long QT Syndrome
MAH	Marketing Authorisation Holder
MATE	Multidrug and Toxin Extrusion Protein
MDCK	Madin Darby Canine Kidney Cell
mg	Milligram
NOAEL	No Observed Adverse Effect Level

Abbreviation	Definition/Description
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Protein
OCT	Organic Cation Transporter
PI	Product Information
PL	Package Leaflet
PSUR	Periodic Safety Update Report
QPPV	Qualified Person Responsible for Pharmacovigilance (in the European Union)
QTcF	Fridericia Correction Factor
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
UGT	UDP-Glucuronosyltransferase
US	United States
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (International Non-proprietary Names [INN] or common name)	Guanfacine
Pharmacotherapeutic group(s) (ATC Code)	Cardiovascular (C02AC02)
Marketing Authorisation Holder	Takeda Pharmaceuticals International AG Ireland Branch
Medicinal products to which this RMP refers	INTUNIV
Invented name(s) in the European Economic Area (EEA)	INTUNIV
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Guanfacine hydrochloride prolonged release tablets (GXR) are available as a once-daily matrix tablet formulation for oral administration only
	Summary of mode of action: Although its mechanism of action in attention-deficit/hyperactivity disorder (ADHD) is unknown, GXR is thought to improve prefrontal cortical cognitive functions, which is theorised to be through post synaptic agonism of α_{2A}-receptors. GXR is readily absorbed and approximately 70% bound to plasma proteins independent of drug concentration. The major route of guanfacine hydrochloride clearance is biotransformation in the liver, with only 30% of the drug being excreted unchanged in the urine. The major metabolite is the 3 hydroxy derivative, which is excreted in the urine as the glucuronide or sulphate conjugate.
	Important information about its 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.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for latest approved PI.

[redacted]

Indication(s) in the EEA	Current: INTUNIV is indicated for the treatment of ADHD in children and adolescents 6-17 years 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, education and social measures
	Proposed: Not applicable
Dosage in the EEA	Current (if applicable): The recommended starting dose is 1 mg of guanfacine, taken orally once a day. Dose should be individualised according to the patient's response and tolerability.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: 1, 2, 3, and 4 mg prolonged-release tablet.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

[redacted]

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

INTUNIV is a non-stimulant indicated as part of a treatment programme for ADHD in paediatric patients (children and adolescents 6-17 years old, inclusive)

<table>
<tr><th colspan="2">Attention-Deficit/Hyperactivity Disorder</th></tr>
<tr><td>Incidence:</td><td>Not applicable</td></tr>
<tr><td>Prevalence:</td><td>A recent systematic review of 175 published studies reported an overall pooled ADHD prevalence estimate for persons 18 years and younger of 7.2%[redacted].
A recent systematic review of Mental Disorders in Europe, including 12 studies in ADHD, reported an estimated mean 12-month prevalence of 5.0% for paediatric patients aged 6-17 years. This equates to approximately 3.3 million 6-17 year old children and adolescents affected by ADHD within the EU member states[redacted].
Polanczyk et al [redacted] estimated the prevalence of ADHD to be 4.8% in Europe among children and adolescents. A six-year follow-up of a large European cohort of children of a mean age of 11.4 years with ADHD showed that the majority (86.5%) still met the DSM-5 diagnostic criteria for this disorder at a mean age of 17.4 years[redacted].
An updated systematic review indicated that variability in prevalence estimates can be explained by methodological differences across studies, however when these factors are controlled for, prevalence estimates in children and adolescents were stable and did not increase between 1985 and 2012 [redacted].
Country-specific prevalence has been estimated for Germany, Netherlands, and Great Britain[redacted]:
<table>
<tr><th colspan="3">Country Specific ADHD Prevalence</th></tr>
<tr><td>Country</td><td>Age Group</td><td>Prevalence</td></tr>
<tr><td rowspan="3">Germany</td><td>7-10 years</td><td>6.4%</td></tr>
<tr><td>11-13 years</td><td>4.6%</td></tr>
<tr><td>14-17 years</td><td>3.9%</td></tr>
<tr><td rowspan="2">Netherlands</td><td>6-8 years</td><td>3.8%</td></tr>
<tr><td>13-18 years</td><td>1.8%</td></tr>
<tr><td>Great Britain</td><td>5-16 years</td><td>2.2%</td></tr>
</table>
The subtypes of ADHD listed in Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) are the Inattentive subtype, the Hyperactive-Impulsive subtype, and the Combined subtype. Most of what is known about ADHD subtype prevalence comes from clinic-based samples. One nationally representative population-based study that included 3082 children 8-15 years of age in the United States (US) estimated that 4.4% (95%CI: 3.2-5.5%) met the DSM-IV criteria for the Inattentive subtype, 2.0% (95%CI: 1.2-2.8%) met the DSM-IV criteria for the Hyperactive-Impulsive subtype, and 2.2% (95%CI: 1.7-2.7%) met the criteria for the Combined subtype [redacted].</td></tr>
<tr><td>Demographics of the target</td><td>Attention-deficit/hyperactivity disorder is a psychiatric condition</td></tr>
</table>

Attention-Deficit/Hyperactivity Disorder	
population in the indication:	that is characterised by inattention, hyperactivity, and impulsivity. In the paediatric population, ADHD is the most frequently encountered neurodevelopmental disorder in primary care settings [redacted]. Attention-deficit/hyperactivity disorder is 2 [redacted] to 3 times [redacted] more prevalent in males than in females. A global systematic review reported that the prevalence of ADHD in children aged 5-19 years was 2.2% and 0.7% for males and females, respectively[redacted]. Although ADHD may first be diagnosed in children younger than 6 years, there is evidence that it persists into adulthood, impairing functioning in about 50% of childhood cases [redacted].
Risk factors for the disease:	Family history of ADHD is the most common risk factor for ADHD in both children and adults, with heritability estimates in children ranging from 79% [redacted] to 88% [redacted] The Larsson study estimated heritability in adults at 72%. Male sex was associated with a 2-fold [redacted] to 3-fold[redacted] increased risk. Preterm birth has been associated with an 83%[redacted] to 97% [redacted] increased risk for a diagnosis of ADHD, with a five-fold increase in risk estimated in adults in a study by Peto et.al[redacted]. Low birthweight has also been associated with a greater than two-fold increase in ADHD risk (OR 2.2, 95% CI 1.17 – 4.20 [redacted], 2.1, 95% CI 1.3 – 3.6 [redacted]. Halmoy also reported that an Apgar score of < 4 at the 5-minute assessment is associated with increased risk of ADHD (OR 2.8, 95% CI 1.2 – 6.8). Maternal use of tobacco during pregnancy was associated with an increased risk for ADHD in both male and female offspring (OR 1.86 95% CI 1.53 – 2.27 and OR 1.67 95% CI 1.07, 2.61, respectively) [redacted]. A statistically non-significant (p=0.06) dose-response in risk of ADHD with cigarette use was observed with a cut point of 10 cigarettes per day (OR 3.0 and 4.8, respectively) . Illicit drug use in the 1-year period pre-delivery was associated with a 5.8-fold increased risk, for ADHD [redacted]. Sagiv found that maternal depression during pregnancy increased risk, with mild to moderate depression during pregnancy was associated with a 7.5-fold increase in risk (95% CI 3.5, 11.6) and severe depression associated with a 9.3-fold increase (95% CI 2.5 – 16.6). Socioeconomic factors that have been associated with risk for ADHD include parental education ranging from 82% [redacted] to 6.8-fold risk [redacted]. Home environment, including quality of support and stimulation was associated with a 5.3-fold increased risk (95% CI 1.5 – 9.3)[redacted]. A recent review paper of ADHD risk factors [redacted] found that estimates for many of the risk factors listed above were not stable, particularly those related to prenatal exposures, and tended to become non-significant as study methodologies incorporated genetic and familial confounds.
The main existing treatment options:	The NICE guidelines suggest For children aged 5 years and over and young people non-pharmacological education and counselling, and environmental modifications are recommended first, followed by pharmacological treatment if symptoms persist in at least one ADHD domain. Methylphenidate should be offered as the first line pharmacological treatment switching to lisdexamfetamine in patients who have had a 6-week trial of methylphenidate at an adequate dose and not derived enough benefit in terms of reduced

[redacted]

Attention-Deficit/Hyperactivity Disorder	
	ADHD symptoms and associated impairment. Consider dexamfetamine for children aged 5 years and over and young people whose ADHD symptoms are responding to lisdexamfetamine but who cannot tolerate the longer effect profile of lisdexamfetamine[redacted]. Treatment with a non-stimulant such as atomoxetine or guanfacine extended release are recommended second line for those that cannot tolerate or do not respond to stimulant therapy. For adolescents (12–18 years of age), it is recommended that first line therapy consist of treatment with an approved stimulant medication for ADHD with the assent of the adolescent. Behavioural therapy may also be prescribed. For patients that do not tolerate or do not respond to stimulant therapy, treatment with a non-stimulant such as atomoxetine or guanfacine extended-release are recommended second line[redacted]. For adults, treatment with a stimulant medication approved for ADHD is recommended first line. For those that do not respond to or cannot tolerate the stimulant medication, treatment with atomoxetine is recommended as second line therapy. As part of a comprehensive treatment plan, behavioural therapy may also be considered a part of first line or second line therapy[redacted]. There are several other EU guidelines which have been published for the management of ADHD, these include European Society for Child and Adolescent Psychiatry, British Association for Psychopharmacology and European Network of Adult ADHD [redacted].
Natural history of the indicated condition in the population, including mortality and morbidity:	ADHD has been shown to have a clear and substantial impact on the lives of those who suffer from this chronic disorder. During childhood, ADHD has been found to interfere with the daily lives of children, parents, and families even more than asthma[redacted]. The main health risks of untreated ADHD are psychosocial morbidity, such as academic, occupational, and interpersonal failure, sexual promiscuity, criminality, and injuries, notably in motor vehicle accidents [redacted]. It has also been observed that untreated paediatric patients with ADHD are at an increased risk of developing a substance-abuse disorder, when compared to non-ADHD controls (Odds ratio=6.3 [1.8-21.6] [redacted]. During adolescence and later school years, ADHD is associated with significant underachievement in reading, increased impairment of school functioning (as reflected in greater absenteeism, grade retention, and school dropout rates[redacted], and greater delinquency [redacted]. Adults with ADHD have been found to have less educational achievement, lower occupational levels, and lower socioeconomic status than predicted based on IQ [redacted]. Finally, ADHD imparts a greater risk of unwanted pregnancy, smoking, alcoholism, substance use disorders, and overt criminality [redacted]. The available literature suggests that young people with an ADHD diagnosis are at increased risk for suicidal behaviour, as compared to their population age group. A review of the literature by [redacted], determined that the rate of completed suicide in males (aged 5-24 years) with ADHD was between 32 and 39 per 100,000 patients per year, which is roughly 3 times greater than in the general population. A separate study using a US managed-care database[redacted]determined that patients with an ADHD diagnosis (adults and children) were nearly 3 times more likely to

[redacted]

[redacted]

Attention-Deficit/Hyperactivity Disorder	
	make a suicide attempt (odds ratio=2.9 95% CI: 2.4, 3.5) than age- and sex-matched controls. A number of factors including comorbid psychiatric disorders appear to heighten the risk for suicidal ideation and behaviour in youth with ADHD. In the US, suicide is the third leading cause of death for young people aged 15-24 years, with notable identified risk factors including difficulty in school, the presence of antisocial or conduct disordered behaviours, or a history of disciplinary or legal problems [redacted]. The findings from the World Health Organization (WHO) European Multi-centre Study of Para-suicide further indicated that young males were at a higher risk of suicide, compared to young females [redacted]. Finally, depression is frequently comorbid with ADHD, and impulsive behaviours related to ADHD along with depression may further compound the risk of suicide in such individuals [redacted].In light of the above risk factors, it is not surprising that a cohort of children meeting DSM-IV-TR criteria for ADHD at age 4-6 years had a significantly increased risk of attempting suicide (hazard ratio 3.60) through age 18 years relative to comparison children[redacted].
Important co-morbidities:	Attention-deficit/hyperactivity disorder may be considered as a spectrum of impairments of cognitive executive functions that often appear together and are often co-morbid with a wide variety of psychiatric disorders, many of which may themselves be spectrum disorders [redacted]. The coexistence of other psychopathology with ADHD is therefore common, and can be subtle and complex. Co-morbidity may encompass a wide variety of disorders, including oppositional defiant and conduct disorder, anxiety and depression, bipolar disorder, learning disorders, social impairment as part of the autism spectrum, tic disorders, problems in sensory motor coordination, and increased risk of smoking and substance abuse [redacted]. Although these co-morbidities may not be direct consequences of ADHD, their increased co-occurrence is relevant in considering safety concerns to the extent that they may require care in the use of stimulants, and in the choice of concomitant medications. Data from the 2007 National Survey of Children's Health (US) documented that co-morbidity is the norm, rather than the exception, within the ADHD paediatric population [redacted]. Based on parental reports for 61 779 children ages 6-17 years, 66.9% of children with ADHD have a co-morbid mental or neurodevelopmental disorder. Major depression and anxiety were found in 13.9 and 17.8% of ADHD children, respectively. Those levels of co-morbidity represent 7- and 8-fold increases in risk associated with ADHD. The below table is taken from [redacted] that lists the prevalence of conditions seen at a higher frequency with ADHD.

Prevalence of Co-Morbid Disorders for Children with ADHD Versus Those Without

	No ADHD (%)	ADHD (%)	Adjusted Relative Risk[a]	95% CI
Learning disability	5.3	46.1 [b]	7.79	6.86-8.86

[redacted]

[redacted]

Attention-Deficit/Hyperactivity Disorder

Conduct disorder	1.8	27.4 [b]	12.58	10.23-15.48
Anxiety	2.1	17.8 [b]	7.45	6.08-9.12
Depression	1.4	13.9 [b]	8.04	6.09-10.62
Speech problem	2.5	11.8 [b]	4.42	3.41-5.73
Autism spectrum disorder	0.6	6.0 [b]	8.72	5.97-12.72
Hearing problem	1.2	4.2 [b]	2.77	1.87-4.11
Epilepsy or seizures	0.6	2.6 [b]	3.93	2.19-7.06
Vision problem	1.4	2.3 [b]	1.47	0.98-2.20
Tourette's syndrome	0.09	1.3 [b]	10.70	4.72-24.23
Any mental health/neurodevelopment disorder	11.5	66.9 [b]	5.12	4.72-5.55

[a] Relative risks were adjusted for child age, sex, race/ethnicity, parent education, household income, and family structure.
[b] P<0.05 for chi-squared test

ADHD=attention-deficit/hyperactivity disorder; CI=confidence interval

The subpopulation of children and adolescents with both ADHD and depression is believed to be a group that is at higher risk for poor psychiatric and social outcomes [redacted].

Suggested pharmacological approaches for treating children and adolescents with depressive disorders are based on relatively few controlled studies, data from adults, and clinical experience.

[redacted]

[redacted]

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity:	
Single and Repeat-dose Toxicity: From the original repeat-dose studies, the no observed adverse effect level (NOAEL) was 1 mg/kg/day for rats and 0.3-1 mg/kg/day for dogs. Higher doses resulted in suppressed body weight gain and food intake as well as some changes in the spleen and liver of dogs and the pancreas and gastrointestinal tract of rats. There were some reductions in red blood cell parameters in both rats and dogs, as well as reductions in cation excretion in dogs; none of these findings were considered to be of clinical significance. Following repeated oral administration of guanfacine, blood glucose levels are decreased in the rat and increased in the dog (3 mg/kg/day). In rats and mice, the incidence of corneal opacity increased with dose (10 and 5 mg/kg/day, respectively). This change was considered to be related to the α-adrenergic activity of guanfacine because clonidine caused the same change at a similar incidence in rats. Similar findings were not apparent at doses up to 3 mg/kg/day in the rat juvenile toxicity studies or in the 52-week dog study.	Repeat dose toxicity studies did not identify any organ toxicity of clinical relevance. No effect was observed in ADHD studies on glucose levels during clinical studies or post-marketing surveillance which could indicate a signal of hyperglycaemia or diabetes mellitus. Corneal opacity has not been reported in clinical use in humans.
Reproductive and Developmental Toxicity: Reproductive toxicology studies performed in rats (male and female fertility, embryofoetal development, pre-and post-natal) and rabbits (embryofoetal development) showed maternal toxicity in both species at high doses (8-10 mg/kg in the rat and 5 mg/kg in the rabbit), with a consequent increase in the incidence of post-implantation loss and reduced offspring survival. However, there was no evidence of teratogenicity. Published data reported foetal developmental delays and a low incidence of exencephalia and spina bifida in mice at guanfacine doses of 1 or 2 mg/kg/day, however, these findings are considered specific to mice which are susceptible to exencephaly and spinal changes following malnutrition during pregnancy. In the main rat juvenile toxicity study guanfacine-related (0.3- 3 mg/kg/day) reductions in body weight gain (with a	Non-clinical studies did not indicate any specific risks of relevance for human exposure in pregnant women or children.

[redacted]

Key Safety Findings	Relevance to human usage
consequent slight delay in development) and slight changes in haematological parameters were generally consistent with findings in the original repeat dose toxicity studies. In a further study conducted to investigate the effects of guanfacine on the development of the eyes and heart, dose related (1 and 3 mg/kg/day) lower body weight gain, abnormal behaviour, increased urination and slightly reduced food consumption were apparent. Ophthalmoscopic examination did not reveal any adverse effects and there was no evidence of any organ weight, macroscopic or microscopic treatment- related findings. In addition, there were no adverse cardiac effects associated with guanfacine. In additional juvenile toxicity studies conducted to investigate concurrent guanfacine (1 mg/kg/day) and methylphenidate (50 mg/kg/day) administration the main findings were reduced body weight gain and behavioural changes, the latter related to methylphenidate treatment. There were no significant adverse effects of either drug alone or in combination on physical or sexual development, motor activity, learning, memory, reproductive performance or on macro- or micro-pathology. 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.
Nephrotoxicity Published literature reported localized necrosis in the renal cortex of rats at 30 mg/kg/day following 5 weeks of dosing and renal necrosis in rats at 10 mg/kg/day following 26 weeks dosing. However, no kidney pathology was noted in the definitive good laboratory practice (GLP) compliant studies of up to 13 weeks in rats (10 mg/kg/day) and 52 weeks in dogs (3 mg/kg/day) as reported in the TENEX® SBA. As nephrotoxicity has not been reported in clinical studies, the relevance of the data in published literature is uncertain.	There are no indications in humans that guanfacine possesses a nephrotoxic potential.
Hepatotoxicity Changes in the liver were limited to hyaline material in hepatocytes, brown pigment in Kupffer cells and increases in Schmorl positive pigment and moderate fatty changes in a	There were no hepatic adverse findings in the non-clinical studies that were considered to be of clinical significance at therapeutic doses.

[redacted]

[redacted]

Key Safety Findings	Relevance to human usage
13-week dog study at 5/10 mg/kg/day and in a 52-week dog study discoloration and centrilobular swelling were observed in the liver at 3 mg/kg/day.	
Genotoxicity Guanfacine was not mutagenic in 4 studies reported in the TENEX SBA – Ames test, micronucleus test, dominant lethal test in male mice and chromosome aberration test in Chinese hamster bone marrow cells. A bacterial reverse mutation test and a chromosome aberration study in human lymphocytes to compare pure and impure guanfacine also proved to be negative.	Based on the weight of evidence from gene mutation assays and studies for chromosomal effects, guanfacine is considered not to have in vivo genotoxic potential.
Carcinogenicity: A 102-week rat study suggested a potential for carcinogenicity with some increases in pancreatic adenomas in high-dose rats. However, after thorough statistical analysis, no significant difference was apparent in pancreatic tumour incidence between the control and high-dose group. Therefore, it was concluded that a carcinogenic potential had not been demonstrated for guanfacine, based on the thorough statistical analysis together with the negative results in a 78-week mouse carcinogenicity study and the 4 mutagenicity studies.	The higher incidence of pancreatic islet adenomas in the 102-week carcinogenicity study are not considered a potential signal because: • More high dose male rats survived to the terminal kill than control males (26 vs 10, respectively) • According to [redacted], this disparity must be considered as part of the statistical analysis to generate valid results • Use of the Mantel-Haenszel method to include the difference in drug exposure times as occurred by the NDA sponsor was appropriate and yielded no difference from control • No hyperplasia of the pancreatic islet cells was noted in either the 26-week rat study [redacted] or in the 1-year dog study • Incidence of pancreatic cell adenomas has been seen in control animals in a 2-year carcinogenicity study conducted at Charles River Laboratories (Charles River Laboratories Compilation of Spontaneous Neoplastic Lesions and Survival in Crl:CD(SD) Rats from Control Groups, 2004) • Negative in genotoxicity tests Therefore, based on the weight of evidence of negative results in mouse and rat carcinogenicity assays, absence of genotoxic potential and the absence of clinical findings, guanfacine is considered not to pose a carcinogenic safety risk to humans.
Safety pharmacology	
General Safety Pharmacology Cardiovascular effects of guanfacine were examined in vitro and in vivo.	Guanfacine is a known antihypertensive agent. By stimulating α_{2A}-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor centre to the heart and blood vessels.

[redacted]

Key Safety Findings	Relevance to human usage
	This results in a decrease in peripheral vascular resistance and a reduction in heart rate.
Bradycardia In conscious telemetered dogs, heart rate was decreased relative to placebo over the 1 to 6 hours post-dosing period following 0.5 mg/kg or 1.5 mg/kg (maximum decreases at 2 hours post-dose -36 bpm and -62 bpm, respectively). This bradycardia was reflected in increases in RR and PR intervals. In 2 dogs, a related worsening of an existing bradydysrhythmia, associated with sinus bradycardia and delayed conduction through the atrioventricular node was observed following a dose of 0.5 or 1.5 mg/kg. No changes in gross morphology or rhythm were noted in 2 further dogs given the same doses where sinus rhythm was normal.	Bradycardia may lead to fatigue and may be associated with syncope. Bradycardia, fatigue and syncope are established adverse reactions observed with GXR. In clinical studies, the mean decreases in heart rate were usually generally small modest and asymptomatic; however, hypotension/bradycardia can occur. Patients who may be taking concomitant medications that can increase the rate and extent of guanfacine exposure may be at an increased risk. In general, age and co-morbid cardiac conditions are key risk factors for bradycardia. Syncopal episodes have the potential to be serious and can result in a physical accident and/or trauma when falling.
Blood pressure Oral administration of 0.5 or 1.5 mg/kg guanfacine did not result in any marked effect on arterial blood pressure (mean systolic or diastolic) in conscious telemetered dogs.	Guanfacine has a blood pressure reducing effect. During the pivotal GXR monotherapy paediatric short-term controlled studies, the maximum mean change from baseline in systolic blood pressure and diastolic blood pressure were -5 and - 3 mmHg for all dose groups combined (generally 1 week after reaching target doses of 1, 2, 3, or 4 mg daily). These changes were dose dependent. Decreases in blood pressure were usually modest and asymptomatic however hypotension can occur. Hypotension occurred in 7% of the GXR group and in 3% of the placebo group. In the adjunctive study, hypotension (3%) was observed in subjects treated with GXR as compared to none in the placebo group. In long-term studies, decreases in systolic and diastolic blood pressure were consistent with those seen in monotherapy studies and became less pronounced over time. **Withdrawal hypertension** Guanfacine suppresses sympathetic outflow resulting in lower blood pressure and following discontinuation subjects may experience an increase in blood pressure due to a rebound in sympathetic outflow. Elevations in blood pressure and heart rate above original baseline (i.e., rebound) have been reported to occur upon discontinuation of GXR. 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 was observed upon discontinuation of INTUNIV. However, individuals may have larger increases than reflected by the mean changes. The

Key Safety Findings	Relevance to human usage
	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.
QT prolongation Guanfacine (1 µg/mL) produced no inhibition of human ether- à-go-go- related gene (hERG) tail currents in the human embryonic kidney 293 (HEK 293 [redacted]) cell line stably transfected with hERG complementary DNA. There was no drug- related changes in electrocardiogram (ECG) and heart rate in a 13-week repeat-dose toxicity study in rats at dose levels of 1, 3, and 10 mg/kg/day. In a 1-year repeat-dose study in dogs receiving 0.3, 1, and 3 mg/kg/day, significant prolongation of QT interval was observed at 1 and 3 mg/kg/day, however, QT interval was not corrected for heart rate in this study, and so the observed prolongation was confounded by reduced heart rate. QT changes were not observed in a GLP compliant cardiovascular study in conscious telemetered dogs at doses of 0.5-1.5 mg/kg using the Fridericia correction factor (QTcF): a pronounced and prolonged bradycardia was observed, coincident with an increase in both RR and PR intervals.	In vitro, guanfacine did not inhibit the hERG potassium channels. Marketing Authorisation Holder (MAH) conducted a thorough QT study, the Global Safety System (GSS) database and a search for reports of potential Torsade de pointes associated with the use of all forms of guanfacine in the Food and Drug Administration (FDA) Adverse Event Reporting System Freedom of Information database to evaluate any potential association of guanfacine with QT prolongation related events. Overall based on the cumulative review of safety data from clinical studies and post-marketing reports, as well as the thorough QT/QTc study in healthy volunteers, there is no evidence of any clinically meaningful effects on ventricular repolarization with GXR.
Sedative events In the dog, antihypertensive doses of guanfacine had low sedative activity.	α_{2A}-receptors may mediate sedation via decreasing sympathetic outflow. Clinically, sedative events are amongst the most common adverse reactions observed with GXR.
Mechanisms for Drug Interactions Guanfacine is metabolized primarily by cytochrome P450 (CYP450) isoenzyme, CYP3A4. Guanfacine did not inhibit nor induce the major human CYPs in vitro. Neither guanfacine nor its 3-hydroxy metabolite significantly inhibited the major human glucuronosyltransferases in vitro and therefore have little potential for clinically significant UDP glucuronosyltransferase (UGT)-mediated drug-drug interactions. Guanfacine is not a substrate for the P-glycoprotein pump, and only elicited a weak inhibitory effect on paclitaxel transport at the highest concentration tested (400 µM). Guanfacine is therefore unlikely to be involved in interactions with other drugs transported by P-glycoprotein.	Guanfacine will likely be subject to drug-drug interactions as a victim if co-administered with potent inhibitors/inducers of CYP3A4. As a perpetrator, guanfacine is unlikely to elicit any drug-drug interactions via CYP, UGT or P-glycoprotein-mediated mechanisms.
CYP Inhibition Additional studies on potential CYP inhibition are described in Table SII.1.	Guanfacine is metabolized 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

[redacted]

Key Safety Findings	Relevance to human usage
	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.
Transporter interactions Additional studies on transporter interactions are described in Table SII.1.	Guanfacine is an *in vitro* inhibitor of multidrug and toxin extrusion protein (MATE)-1 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 organic cation transporter (OCT) 1 at maximal portal vein concentrations. Concomitant administration of guanfacine with OCT1 substrates with a similar t_{max} (e.g., metformin) may result in guanfacine acting as a perpetrator of drug interaction, with a possible increase in peak plasma concentration (C_{max}) of these other medicinal products

Potential for Drug Interactions-Additional Studies

New secondary pharmacology and metabolism studies have been conducted to evaluate the pharmacological activity of 3-OH-guanfacine, the 3-hydroxy metabolite of guanfacine, and to further investigate the potential for CYP (cytochrome P450) inhibition and/or induction and potential transporter interactions (Table SII.1).

Table SII.1. Additional Non-clinical studies for potential drug interactions

Study Number	Type of Study	Test System	Objectives
Pharmacokinetics			
V7089M-SPD503	In vitro transporter interaction study	HEK cell lines transfected with transporters of interest, colorectal adenocarcinoma cells (CACO-2) brush border expressing cell (C2BBe1), breast cancer resistance protein (BCRP)- Madin Darby canine kidney cell (MDCK), and MDCK cells	To evaluate the substrate and/or inhibitor potential of guanfacine for the following transporters: • BCRP • organic anion transporting protein (OATP)1B1 and OATP1B3 • organic anion transporter (OAT1) and OAT3 • OCT1 and OCT2 • MATE1 and MATE2K • bile salt export pump (BSEP) • MRP2

[redacted]

Study Number	Type of Study	Test System	Objectives
V7401M-SPD503	In vitro time-dependent CYP inhibition study	Pooled human hepatic microsomes and pooled human intestinal microsomes	To determine the half maximal inhibitory concentration (IC_{50}) values of guanfacine for inhibition of: • CYP2B6; • Intestinal CYP3A4; To identify if guanfacine is a time-dependent inhibitor ofCYP1A2, 2C9, 2C19, 2D6 and hepatic 3A4/5
V7400M-SPD503[a]	In vitro CYP induction study	Fresh human hepatocytes from 3 donors	To identify if guanfacine can induce CYP enzymes.
V8953M-SPD503	In vitro uptake in hepatocytes	Fresh human hepatocytes from 3 donors	To identify potential rate-limiting step of guanfacine by OCT1
Secondary Pharmacodynamics			
V7613M-SPD503	Intrinsic efficacy of 3-OH guanfacine at α_2 receptor subtypes	In vitro	To assess the pharmacological activity of the 3-hydroxy metabolite of guanfacine, on α_{2A2} α_{2B} and α_{2C} adrenoceptors in vitro

[a] Study V7400M-SPD503 was re-performed to align with current EMA guideline on drug-drug interactions

The findings confirmed that guanfacine is not an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 in vitro and it is not a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6, or CYP3A. However, low-potency time-dependent inhibition of CYP2C19 cannot be ruled out due to the IC_{50} shift could not be determined. There was no evidence of induction of the enzyme activities associated with CYP3A4 by guanfacine, although minimal induction of enzymes of the CYP1A2 and CYP2B6 subfamilies were observed in 1 of 3 human liver donor samples used. Guanfacine is therefore unlikely to affect the metabolism of any co-administered drugs during clinical use, however, as guanfacine is metabolised by CYP3A4, potent inhibitors or inducers of this enzyme are likely to affect the clearance of guanfacine itself, resulting in altered plasma levels of guanfacine in man. Clinical drug-drug interaction studies demonstrated this with ketoconazole and rifampin. Physiologically-based pharmacokinetic analysis indicated that significant increases in the systemic exposure of guanfacine would be anticipated following oral administration of guanfacine in the presence of moderate CYP3A4 inhibitors and significant decrease in the systemic exposure of guanfacine would be anticipated following oral administration of guanfacine in the presence of moderate CYP3A4 inducers. Therefore, dosage adjustments are recommended with concomitant use of strong or moderate CYP3A4 inhibitors or inducers.

In vitro, 3-OH-guanfacine, showed no evidence of agonist or antagonist activity on α_{2A}, α_{2B} and α_{2C} human adrenoreceptors.

Neither guanfacine nor its 3-hydroxy metabolite significantly inhibited the major human glucuronosyltransferases in vitro and therefore have little potential for clinically significant UGT-mediated drug-drug interactions.

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.

For hepatic-mediated clearance of guanfacine, metabolic clearance is likely the rate limiting step, therefore there is no significant systemic exposure increase to guanfacine, as a victim of drug interaction, is anticipated when OCT1 is inhibited.

[redacted]

The Marketing Authorisation Holder (MAH) considers the available non-clinical data continue to support the use of guanfacine in of treatment of ADHD in children and adolescents aged 6-17 years.

Conclusion on Non-clinical data

There are no safety concerns specifically arising from the non-clinical evaluation of guanfacine hydrochloride prolonged release tablets (GXR) that are not adequately addressed by the extensive clinical study and post-marketing clinical data available. Therefore, MAH considers there is no need for additional non-clinical data.

Part II: Module SIII - Clinical trial exposure

Brief Overview of Development

The clinical development program for GXR conducted by MAH for the treatment of ADHD in children and adolescents (aged 6-17 years) included 2 Phase 1 studies and 13 Phase 2-4 studies conducted in children and adolescents with ADHD. In addition, 12 Phase 1 studies were conducted in healthy adult volunteers.

The following studies were conducted in children and adolescents with ADHD: SPD503-107, SPD503-113, SPD503-205, SPD503-206, SPD503-301, SPD503-303, SPD503-304, SPD503-305, SPD503-307, SPD503-312, SPD503-313, SPD503-314, SPD503-315, SPD503-316 and SPD503-318. Study SPD503-303 is an open-label extension of SPD503-301, and SPD503-305 is an open-label extension of studies SPD503-205/SPD503-304. Study SPD503-318 was an open-label study that included European subjects who participated in SPD503-315 and SPD503-316.

The following studies were sponsored and conducted by Shionogi in Japan: 1209A3111, 1506A3112, and 1608A3113, 1306A3122 and 1307A3131. Studies 1209A3111, 1506A3112 and 1608A3113 were pharmacokinetic studies conducted in healthy adults. Study 1306A3122 was conducted in children and adolescents with ADHD. Study 1307A3131 is a long-term extension study that includes subjects who participated in 1306A3122. Safety information for these studies was not included in the studies pool presented in the tables below.

Table SIII.1: Duration of exposure (All indications)

Cumulative for all indications (person time)*:		
Duration of exposure	**Patients**	**Person time**
At least 1 day	2,894	1,216.10
At least 7 days	2,837	1,215.70
At least 28 days	2,261	1,192.60
At least 90 days	1,071	1,003.00
At least 180 days	564	849.36
At least 545 days	289	606.29
At least 730 days	173	388.80
Total person time	**1,216.10**	

Note: Subject-time is calculated as the total exposure for all subjects, converted to years (total exposure/365.25).
DLP 31-July-2018
*The numbers exclude the SPD503-401 study as the study is blinded

Person time per indication:				
ADHD (All Studies)				
	ADHD ≤1 year	**ADHD >1 year but ≤2 years**	**ADHD >2 years but ≤5 years**	**ADHD >5 years**
Duration of exposure	**Number of Subjects**			
At least 1 day	1,063	216	619	522
At least 7 days	1,044	213	611	510
At least 28 days	966	191	559	466
At least 90 days	531	77	242	219
At least 180 days	299	45	122	97

[redacted]

Person time per indication:				
ADHD (All Studies)				
At least 365 days	191	39	82	64
At least 545 days	144	29	64	51
At least 730 days	81	18	41	33
Total Subject-time (years)	579.53	109.35	281.78	223.3

Note: The duration of ADHD is from the time of diagnosis to enrolment in study; DLP 31-July-2018
Subject-time is calculated as the total exposure for all subjects, converted to years (total exposure/365.25).

Table SIII.2: Age group and gender (All Studies)*

Cumulative for all age/gender groups (person time):		
Age group	**Subjects**	**Subject-time (years)**
Children (6-12 years)	1,727	851.46
Adolescents (13-17 years)	696	344.75
Adults (≥18 years)	471	19.89
Male	2001	896.79
Female	893	319.31
Children (6-12 years) - male	1,238	644.30
Children (6-12 years) - female	489	207.16
Adolescents (13-17 years) - male	486	241.92
Adolescents (13-17 years) - female	210	102.83
Adults (≥18 years) - male	277	10.57
Adults (≥18 years) - female	194	9.32

Note: Subject-time is calculated as the total exposure for all subjects, converted to years (total exposure/365.25).
DLP 31-July-2018
*The numbers exclude the SPD503-401 study as the study is blinded.

Table SIII.3: Dose (All Studies)*

Cumulative for all doses of exposure (person time):		
Dose of exposure	**Patients**	**Person time**
GXR 1 mg/day	2,442	119.23
GXR 2 mg/day	2,490	264.58
GXR 2.5 mg/day	48	1.31
GXR 3 mg/day	1982	362.15
GXR 4 mg/day	1563	368.96

[redacted]

[redacted]

Cumulative for all doses of exposure (person time):		
Dose of exposure	**Patients**	**Person time**
GXR 5 mg/day	233	52.14
GXR 6 mg/day	106	41.51
GXR 7 mg/day	39	6.06
GXR 9 mg/day	9	0.17
Total	**2,894**	**1,216.10**

Subject-time is calculated as the total exposure for all subjects, converted to years (total exposure/365.25). DLP 31-July-2018
In studies where subjects received more than 1 dose (while tapering up or down) exposure to each dose alone is counted. The total exposure to each dose does not necessarily equal the total exposure to GXR. GXR=guanfacine hydrochloride prolonged release tablets.
*The numbers exclude the SPD503-401 study as the study is blinded.

Table SIII.4: Ethnic origin (All indications)*

Ethnic origin	**Patients**	**Person time**
White	1,937	950.72
Black or African American	529	136.93
Asian/Native Hawaiian or Other Pacific Islander	29	18.87
American Indian or Alaska Native	14	2.93
Other	367	94.81
Missing	18	11.85
Total	**2,894**	**1,216.10**

Note: Subject-time is calculated as the total exposure for all subjects, converted to years (total exposure/365.25). DLP 31-July-2018
*The numbers exclude the SPD503-401 study as the study is blinded.

[redacted]

[redacted]

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

Current co-morbid psychiatric diagnosis (except Oppositional Defiant Disorder)	
Reason for exclusion:	Patients with significant co-morbid psychiatric diagnoses were excluded in order to avoid the potential for confounding the interpretation of study results.
Is it considered to be included as missing information?:	No
Rationale:	Attention-deficit/hyperactivity disorder may be considered as a spectrum of impairments of cognitive executive functions that often appear together and are often co-morbid with a wide variety of psychiatric disorders, many of which may themselves be spectrum disorders. Co-morbidity may encompass a wide variety of disorders, including oppositional defiant and conduct disorder, anxiety and depression, bipolar disorder, learning disorders, social impairment as part of the autism spectrum, tic disorders, problems in sensory motor coordination, and increased risk of smoking and substance abuse. Patients with significant co-morbid psychiatric disorders that could confound study results were excluded. Patients with co-morbid symptoms inclusive of the above spectrum were not necessarily excluded, and subjects could have co-morbid diagnoses of oppositional defiant disorder.

Patients <6 years of age	
Reason for exclusion:	The results of available studies in pre-school children using short-acting stimulants, or atomoxetine indicate that there is limited benefit in treating young children. Due to formulation technical reasons, GXR cannot be formulated in smaller tablets than 1 mg, which limits the possibility of titration in very young children.
Is it considered to be included as missing information?:	No
Rationale:	The indication for use will be in 6-17-year-olds inclusive and Summary of Product Characteristics (SmPC) will indicate that the safety and efficacy of GXR in paediatric patients <6 years of age have not been established.

[redacted]

Clinically important abnormality on urine drug and/or alcohol screen at the Screening Visit or subjects who had a history of alcohol or other substance abuse or dependence.	
Reason for exclusion:	It is considered potentially unsafe for these subjects to be enrolled in clinical studies; exclusion is not specific to GXR.
Is it considered to be included as missing information?:	No
Rationale:	These restrictions are common to most clinical studies. Such patients should be managed according to the clinical judgment of the treating physician.

Subject was significantly overweight at the Screening.	
Reason for exclusion:	Patients with obesity are more likely to have significant co-morbid medical illness including high blood pressure and high cholesterol (which are risk factors for cardiovascular disease). The safety and efficacy of GXR in patients with cardiovascular disease has not been systematically studied in controlled clinical studies.
Is it considered to be included as missing information?:	No
Rationale:	These restrictions are common to most clinical studies and such patients should be managed according to the clinical judgment of the treating physician.

Subject had any condition or illness including clinically significant abnormal laboratory values at Screening which, in the opinion of the investigator, represented an inappropriate risk to the subject and/or could have confounded the interpretation of the study.	
Reason for exclusion:	It is considered potentially unsafe for these subjects to be enrolled in clinical studies; exclusion is not specific to GXR.
Is it considered to be included as missing information?:	No
Rationale:	These restrictions are common to most clinical studies. Such patients should be managed according to the clinical judgment of the treating physician.

Subject was currently considered a suicide risk in the opinion of the investigator, had previously made a suicide attempt, or had a prior history of, or was currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation were not necessarily excluded, based on the assessment of the investigator.	
Reason for exclusion:	It is considered potentially unsafe for these subjects to be enrolled in clinical studies;

[redacted]

[redacted]

Subject was currently considered a suicide risk in the opinion of the investigator, had previously made a suicide attempt, or had a prior history of, or was currently demonstrating active suicidal ideation. Subjects with intermittent passive suicidal ideation were not necessarily excluded, based on the assessment of the investigator.	
	exclusion is not specific to GXR.
Is it considered to be included as missing information?:	No
Rationale:	These restrictions are common to most psychiatry studies. Such patients should be managed according to the clinical judgment of the treating physician.

Subject had clinically significant ECG findings, a known history or presence of structural cardiac abnormalities, serious heart rhythm abnormalities, syncope, cardiac conduction problems (e.g., clinically significant heart block), exercise related cardiac events including syncope and pre syncope, or clinically significant bradycardia.	
Reason for exclusion:	It is considered potentially unsafe for these subjects to be enrolled in clinical studies; exclusion is not specific to GXR.
Is it considered to be included as missing information?:	No
Rationale:	These restrictions are common to most clinical studies. As the majority of bradycardia events observed in clinical studies were non-serious and mild to moderate in severity, such patients should be managed according to the clinical judgment of the treating physician. Syncope and bradycardia are known risks with INTUNIV.

Subject with orthostatic hypotension or a known history of hypertension.	
Reason for exclusion:	Guanfacine is a known antihypertensive agent. The safety and efficacy of GXR in patients with cardiovascular disease has not been systematically studied in controlled clinical studies.
Is it considered to be included as missing information?:	No
Rationale:	Hypotension/decreased blood pressure is a known risk with INTUNIV.

Subject had a history of a seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years) or the presence of a serious tic disorder including Tourette's syndrome.	
Reason for exclusion:	Patients with significant co-morbid medical or psychiatric diagnoses were excluded in order to avoid the potential for confounding the interpretation of study results. Severe tics may be mistaken for hyperactivity and impulsivity,

[redacted]

[redacted]

Subject had a history of a seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years) or the presence of a serious tic disorder including Tourette's syndrome.	
	and some seizures may mimic inattention/day dreaming i.e., absence.
Is it considered to be included as missing information?:	No
Rationale:	Such patients should be managed according to the clinical judgment of the treating physician.

Current use of any prohibited medication or other medications, including herbal supplements, that affect blood pressure or heart rate or that have Central nervous system (CNS) effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (inhaled bronchodilators are permitted) or a history of chronic use of sedating medications (i.e., antihistamines) in violation of the protocol specified washout criteria at the Baseline Visit.	
Reason for exclusion:	Guanfacine is a known antihypertensive agent. The safety and efficacy of GXR in patients with cardiovascular disease has not been systematically studied in controlled clinical studies. The use of medications that have sedative effects have the potential for confounding the interpretation of study results.
Is it considered to be included as missing information?:	No
Rationale:	Such patients should be managed according to the clinical judgment of the treating physician. Withdrawal blood pressure increase, bradycardia and sedative events is a known risk with INTUNIV.

Subjects who are pregnant or breastfeeding women	
Reason for exclusion:	It is considered potentially unsafe for these subjects to be enrolled in clinical studies; exclusion is not specific to GXR.
Is it considered to be included as missing information?:	Yes
Rationale:	Not applicable

Subjects with clinically significant hepatic or renal impairment.	
Reason for exclusion:	The impact of hepatic or renal impairment on the pharmacokinetics of GXR in children has not been assessed. Dose reduction may be required in patients with clinically significant impairment of hepatic and/or renal function.
Is it considered to be included as missing information?:	Yes

[redacted]

[redacted]

Subjects with clinically significant hepatic or renal impairment.	
Rationale:	Not applicable

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	There is limited or no data from the use of guanfacine in pregnant women. Studies in animals have shown reproductive toxicity. INTUNIV is not recommended during pregnancy and in women of childbearing potential not using contraception. There are no or limited data on the use of GXR in women who are breastfeeding. Available pharmacodynamic and toxicological data in animals have shown excretion of guanfacine and its metabolites in milk. It is unknown whether guanfacine is excreted in human milk. 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 GXR therapy for the woman. There are no or limited amount of data regarding effect on fertility from the use of GXR in humans. Animal studies indicate an effect on male fertility.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	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 (Glomerular filtration rate [GFR] 15-29 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 to 17 years old) has not been assessed. Guanfacine is a known antihypertensive agent. By stimulating α_{2A}-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor centre to the heart and blood vessels. This results in a decrease in

[redacted]

Type of special population	Exposure
	peripheral vascular resistance and a reduction in blood pressure and heart rate. The safety and efficacy of GXR in patients with cardiovascular disease have not been systematically studied in controlled clinical studies.

[redacted]

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

For INTUNIV, the methodology used to calculate the exposure assumes a defined daily dose (DDD) of 3 mg (based on WHO Anatomical Therapeutic Chemical (ATC)/DDD index 2019).

Patient Exposure Calculation: (Total mgs/DDD)/365 = Number of patient-years.

SV.1.2. Exposure

Based on the above methodology, the patient exposure can be estimated to be 964.9 million DDDs cumulatively, corresponding to approximately 2,220,284 patient-years of treatment cumulatively till December-2022.

[redacted]

[redacted]

[redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Guanfacine has no known potential for abuse or dependence. Guanfacine is a well characterised highly selective α_{2A}-adrenergic receptor agonist first approved as an antihypertensive medication. The drug received marketing approval in the EU in some countries (Netherlands, Ireland) as early as 1979, and was subsequently approved by several other countries under the brand names Entulic, Tenex, Akfen, and Cifagrin. These drugs have not emerged as drugs of abuse or dependence in any population despite decades of monitoring by a variety of surveillance systems.

[redacted]

[redacted]

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

None.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
Bradycardia	Bradycardia has been reported with GXR in clinical trials, the post-marketing setting and scientific literature. Clinical trial data shows a decrease in heart rate was usually modest and asymptomatic however, bradycardia can occur. Guanfacine is a known antihypertensive agent. Bradycardia may lead to extreme fatigue and predispose a patient to syncope.
Syncope	Syncope has been observed with GXR in clinical trials, the post-marketing setting and scientific literature. Syncope can be serious, resulting in a physical accidents and/or trauma.
Hypotension/decreased blood pressure	Hypotension/decreased blood pressure has been observed in clinical trials with GXR. The severity can range from mild to moderate. Clinical studies show the decreases in blood pressure were usually modest and asymptomatic however, hypotension can occur.
Withdrawal blood pressure increase	Withdrawal blood pressure increase has been observed in clinical trials with GXR. Blood pressure increase, due to an abrupt discontinuation of GXR may be complicated, in rare instances, by hypertensive emergencies, including hypertensive encephalopathy. There is a hypothetical risk for hypertensive crisis in subjects with existing hypertension.
Sedative events	Sedative events have been observed in clinical trials with GXR. Sedative events can be severe, resulting in a physical accident and/or trauma.
Weight Increase	Weight increase has been observed in clinical trials with GXR. People who are overweight or obese are at risk for developing diabetes and cardiovascular disease

Important Potential Risks	Risk-benefit impact
QT prolongation	Drug induced QT prolongation is a serious condition that can be fatal. QT prolongation has been observed in clinical trials with INTUNIV and many of the events were moderate in severity.
Off-label use	Children under the age of 6 years may react with hypotension, tiredness and sedative events. Off-label use has been observed in the post-marketing setting, with the majority of side effects are of a non-serious character.

Missing Information	Risk-benefit impact
Use in pregnant or breastfeeding women	There is limited information available about the long-term use of GXR in patients with ADHD. Non-clinical studies have shown foetal and maternal toxicity. GXR should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk to the foetus.
Use in patients with hepatic or renal impairment	There is limited information available about the long-term use of GXR in patients with ADHD. Guanfacine in adults is cleared both by the liver and the kidney and approximately 50% of the clearance of guanfacine is hepatic. It may be necessary to adjust the dose in patients with significant impairment of renal function.
Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	There is limited information available about the long-term use of GXR in patients with ADHD.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

"Bradycardia, syncope, hypotension, withdrawal blood pressure increase, sedative events, and weight increase" which are classified as important identified risks are removed from the list of safety concerns

Justification: As per the PRAC assessment report (Procedure No. EMEA/H/C/003759/II/0033/G), the assessors consider that the additional risk minimisation measures included in the RMP of the INTUNIV should be deleted. Subsequently, the following important identified risks (i.e., bradycardia, syncope, hypotension, withdrawal blood pressure increase, sedative events, and weight increase) should be removed from the RMP since there is no need for further aRMMs and routine pharmacovigilance activities are considered appropriate to keep monitoring them.

MAH response: The MAH acknowledges the above recommendation and the important identified risks have been removed from the subsequent sections of the RMP.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: QT prolongation	
Potential mechanisms:	In vitro, guanfacine did not inhibit the hERG potassium channels. By stimulating α_{2A}-adrenergic receptors, GXR reduces sympathetic nerve impulses from the vasomotor centre to the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate. The reduced heart rate leads to an increased QT-time. Thus, an apparent increase in mean QT is observed. Heart rate correction methodologies, such as the Bazett's or Fridericia's formulae, do not fully correct for the heart rate variability observed during a dosage interval. However, guanfacine does not appear to interfere with cardiac repolarisation of the form associated with pro-arrhythmic drugs.
Evidence source(s) and strength of evidence:	QT prolongation has been reported in clinical trials and post-marketing
Characterisation of the risk:	Long QT syndrome (LQTS) is a disturbance of cardiac rhythm that can be either congenital or can be acquired (due to

[redacted]

Important Potential Risk: QT prolongation	
	disturbances in blood electrolytes or due to various drugs). It is an important cause of malignant ventricular arrhythmias and sudden cardiac death in young individuals with otherwise normal cardiac morphology. The prevalence of LQTS is relevant as the background incidence for possible drug-induced long QT. The background prevalence of LQTS in the ADHD and general paediatric population(s) was researched through a combination of electronic searches of the medical literature using Medline. True congenital QT prolongation appears to be very rare in the general population of children and adolescents. A study of 7,961 Japanese school children (mean age, 9.9+/-3.0 years) who were screened by ECG, found the prevalence of likely LQTS (LQTS score <=3.5) to be 0.038% [redacted]. A similar result has been seen in another study of Japanese children[redacted]. The prevalence of QT prolongation in 71,855 elementary school children (aged 5-6 years) and 80,467 junior high student (aged 12-13 years) was estimated to be 0.027% in females and 0.020% in males. No published reports on the incidence or prevalence of LQTS in children with diagnosed ADHD (independent of drug exposure) were found in this literature review. The incidence of QT prolongation with GXR in all randomized double-blind phase 2-4 clinical studies was 0.4%. All QT prolongation events were non-serious, mild to moderate in severity and all, but one event resolved. **Post-marketing data as of DLP 17-March-2023:** Through 17-March-2023, the post-marketing reporting rate of QT Prolongation coincident with INTUNIV therapy is estimated to be 0.05/1000 patient-years in patients with ADHD. *Frequency parameter:* Cumulatively 117 cases with 117 events were reported for this risk. *Seriousness/outcome:* Of the 117 events received, all events were serious. Outcome of the events reported were: Fatal (2), not resolved (8), resolved (62), resolving (11) and unknown (34).
Risk factors and risk groups:	Risk factors for LQTS that have been identified in children include female gender, age, prior syncopal history, QT interval duration, and genetic/familial factors [redacted]. Most research in this area has focused upon the risk factors for serious cardiac events following diagnosis of LQTS.
Preventability:	The following statements in the SmPC are intended to reduce the risk of QT prolongation among patients who are prescribed GXR: 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. INTUNIV causes a decrease in heart rate. Given the effect of INTUNIV on heart rate, the concomitant use of INTUNIV with QT

[redacted]

[redacted]

Important Potential Risk: QT prolongation	
	prolonging medicinal products is generally not recommended.
Impact on the risk-benefit balance of the product:	QT prolongation will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The benefit-risk profile of GXR remains positive.
Public health impact:	In clinical studies, the majority of events were moderate in severity. All events were non-serious, and all except 1 resolved. The potential impact on public health appears to be low.

SVII.3.2. Presentation of the missing information

Use in pregnant or breastfeeding women	
Evidence source:	There are no adequate, well-controlled studies of INTUNIV in pregnant women. Data experiments have shown that guanfacine crosses the placenta. However, administration of guanfacine to rats and rabbits at 2 and 2.7 times, respectively, the maximum recommended human dose of 0.12 mg/kg/day on a mg/m^2 basis, resulted in no evidence of harm to the foetus. Higher doses (13.5 times the maximum recommended human dose in both rabbits and rats) were associated with reduced foetal survival and maternal toxicity[redacted]. There are no clinical data on the use of INTUNIV in women who are breastfeeding. In non-clinical studies, guanfacine was excreted into rat milk. It is not known if guanfacine would also be excreted into human milk. GXR is indicated for treatment of ADHD in paediatric patients at age 6 to 17 years old. The GXR exposure during pregnancy in both clinical trials and post marketing data is very rare.
Population in need of further characterisation	Monitor and evaluate the safe use of INTUNIV during pregnancy and lactation.

Use in patients with hepatic or renal impairment	
Evidence source:	Guanfacine is cleared both by the liver and the kidneys, and approximately 50% of the clearance of guanfacine is hepatic. In adult patients with impaired renal function, the cumulative urinary excretion and renal clearance of guanfacine diminished as renal function decreased. The impact of hepatic or renal impairment on the pharmacokinetics of guanfacine in paediatric patients (children and adolescents 6-17 years old inclusive) was not assessed. Dose reduction may be required in patients with clinically significant impairment of hepatic and/or renal function.
Population in need of further characterisation	Monitor and evaluate the safe use of INTUNIV in patients with renal or hepatic impairment.

Long-term safety (neurocognition in particular but also effects on growth, sexual maturation)	
Evidence source:	There is limited information available about the long-term use of INTUNIV in patients with ADHD.
Population in need of further characterisation	Monitor and evaluate the long-term safe use of INTUNIV in patients especially effects on neurocognition, effect on growth

[redacted]

[redacted]

Long-term safety (neurocognition in particular but also effects on growth, sexual maturation)	
	and sexual maturation.

[redacted]

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• QT prolongation
Missing information	• Use in pregnant or breastfeeding women • Use in patients with hepatic or renal impairment • Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

None.

Other forms of routine pharmacovigilance activities

None.

III.2. Additional pharmacovigilance activities

SPD503-401 A Clinical study SPD503-401: A Comparative Safety Study of INTUNIV in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) according to an agreed protocol
Study short name and title: SPD503-401 A Clinical study SPD503-401: A Comparative Safety Study of INTUNIV in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) according to an agreed protocol
Rationale and study objectives: **Rationale**: Study SPD503-401 is required post approval safety study and has been designed to evaluate the long-term safety and efficacy of SPD503 with focus on neurocognition, growth, and sexual maturation in children and adolescents with ADHD. **Primary Objective**: To evaluate TAK-503 compared with atomoxetine after 12 months of once daily (QD) treatment on psychomotor speed and attention as measured by the Cambridge automated neuropsychological test battery (CANTAB) reaction time (RTI) task, using the mixed-effects model for repeated measures (MMRM). The effect of TAK-503 on cognition will be assessed and interpreted on the totality of the data. **Secondary objectives**: Assessment of cognitive domain as measured by CANTAB; - Long term evaluation of growth, sexual maturation, sedative effects; - other related safety and efficacy endpoints.
Study design: Protocol SPD503-401 will be conducted in 2 parts. Study Part A will be a randomized, double-blind, multicentre, parallel-group, dose-optimization, safety evaluation of SPD503 in comparison with atomoxetine. Study Part B will be open-label safety evaluation of SPD503. In Study Part A, an atomoxetine arm has been included as an active comparator and a placebo treatment arm for noninferiority and assay sensitivity analysis respectively.
Study population: Approximately 288 children and adolescents diagnosed with ADHD by DSM-V will be enrolled where approximately 25% will be aged 13 to 17 years and at least 25% will be female.
Milestones: Protocol Submission: 29-July-2016 Submission of final study report: 31-January-2028

[redacted]

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
SPD503-401: A Comparative Safety Study of INTUNIV in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) according to an agreed protocol (Category 1) On-going	**Primary Objective**: To evaluate TAK-503 compared with atomoxetine after 12 months of QD treatment on psychomotor speed and attention as measured by the Cambridge automated neuropsychological test battery (CANTAB) reaction time (RTI) task, using the mixed-effects model for repeated measures (MMRM). The effect of TAK-503 on cognition will be assessed and interpreted on the totality of the data. **Secondary objectives**: Assessment of cognitive domain as measured by CANTAB; - Long term evaluation of growth, sexual maturation, sedative effects; - other related safety and efficacy endpoints	Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	Protocol submission Final study report	29-July-2016 31-January-2028
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities				
Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

[redacted]

[redacted]

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the PI is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
QT prolongation	**Routine risk communication:** SmPC Section 4.2, 4.4 and 4.5 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 – Recommendations to conduct a baseline evaluation at pre-treatment screening SmPC Section 4.4 – Caution when guanfacine is prescribed to patients with a known history of QT prolongation. Recommended to monitor of heart rate. SmPC Section 4.5 - Caution of any additive effect to INTUNIV. INTUNIV with QT prolonging medicinal products is generally not recommended **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Use in pregnant or breastfeeding women	**Routine risk communication:** SmPC Section 4.6 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 – INTUNIV is not recommended during pregnancy. 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 PL Section 2 – Patients that are pregnant or breastfeeding, think they may be pregnant or planning on having a baby, should ask their doctor or pharmacist for advice. Patients should not take this medicine if they are pregnant or breastfeeding **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine
Use in patients with renal or hepatic impairment	**Routine risk communication:** SmPC Section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 – Dose reduction may be required for patients with hepatic and renal impairment.

[redacted]

[redacted]

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Prescription only medicine
Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	**Routine risk communication:** SmPC Section 4.2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 – It is advised that patients should be re-evaluate the usefulness of the medication when guanfacine used for extended periods (over 12 months). **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
QT prolongation	**Routine risk minimisation measures:** SmPC Section 4.2 – Posology and method of administration SmPC Section 4.4 - Special warnings and precautions for use SmPC Section 4.5 - Caution of any additive effect to INTUNIV. INTUNIV with QT prolonging medicinal products is generally not recommended Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use in pregnant or breastfeeding women	**Routine risk minimisation measures:** SmPC Section 4.6 – INTUNIV is not recommended during pregnancy. 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

[redacted]

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL Section 2 – Patients that are pregnant or breastfeeding, think they may be pregnant or planning on having a baby, should ask their doctor or pharmacist for advice. Patients should not take this medicine if they are pregnant or breastfeeding Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.	
Use in patients with hepatic or renal impairment	**Routine risk minimisation measures:** SmPC Section 4.2 – Dose reduction may be required for patients with hepatic and renal impairment. Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	**Routine risk minimisation measures:** SmPC Section 4.2 – It is advised that clinician should periodically re-evaluate the long-term usefulness of the medication when guanfacine used for extended periods (over 12 months) Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Clinical Study SPD503-401

[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for INTUNIV (guanfacine)

This is a summary of the risk management plan (RMP) for INTUNIV. The RMP details important risks of ITUNIV, how these risks can be minimised, and how more information will be obtained about 's risks and uncertainties (missing information).

INTUNIV's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how INTUNIV should be used.

This summary of the RMP for INTUNIV should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of INTUNIV's RMP.

I. The medicine and what it is used for

INTUNIV is authorised for attention deficit hyperactivity disorder (see SmPC for the full indication). It contains guanfacine as the active substance and it is given orally.

Further information about the evaluation of INTUNIV's benefits can be found in INTUNIV's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https:/www.ema.europa.eu/en/medicines/human/EPAR/intuniv.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of INTUNIV, together with measures to minimise such risks and the proposed studies for learning more about INTUNIV's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - include PSUR statement only if product has PSUR requirements so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of INTUNIV is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of INTUNIV are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of INTUNIV. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	• QT prolongation
Missing information	• Use in pregnant or breastfeeding women • Use in patients with hepatic or renal impairment • Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)

II.B Summary of important risks

Important potential risk: QT prolongation	
Evidence for linking the risk to the medicine	QT prolongation has been reported in clinical trials and post-marketing
Risk factors and risk groups	Risk factors for that have been identified in children include female gender, age, prior syncopal history, QT-interval duration, and genetic/familial factors. Most research in this area has focused upon the risk factors for serious cardiac events following diagnosis of LQTS.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, 4.4 and 4.5 Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information: Use in pregnant or breastfeeding women	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 PL Section 2. Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing information: Use in patients with hepatic or renal impairment	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2. Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance	**Additional pharmacovigilance activities:** None

[redacted]

Missing information: Use in patients with hepatic or renal impairment	
activities	

Missing information: Long term safety (neurocognition in particular but also effects on growth, sexual maturation)	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2. Prescription only medicine **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** SPD503-401 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study name	Purpose of the study
SPD503-401: A Comparative Safety Study of INTUNIV in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) according to an agreed protocol	Study SPD503-401 is required post approval safety study and has been designed to evaluate the long-term safety and efficacy of SPD503 with focus on neurocognition, growth, and sexual maturation in children and adolescents with ADHD.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for INTUNIV.

[redacted]

[redacted]

Part VII: Annexes

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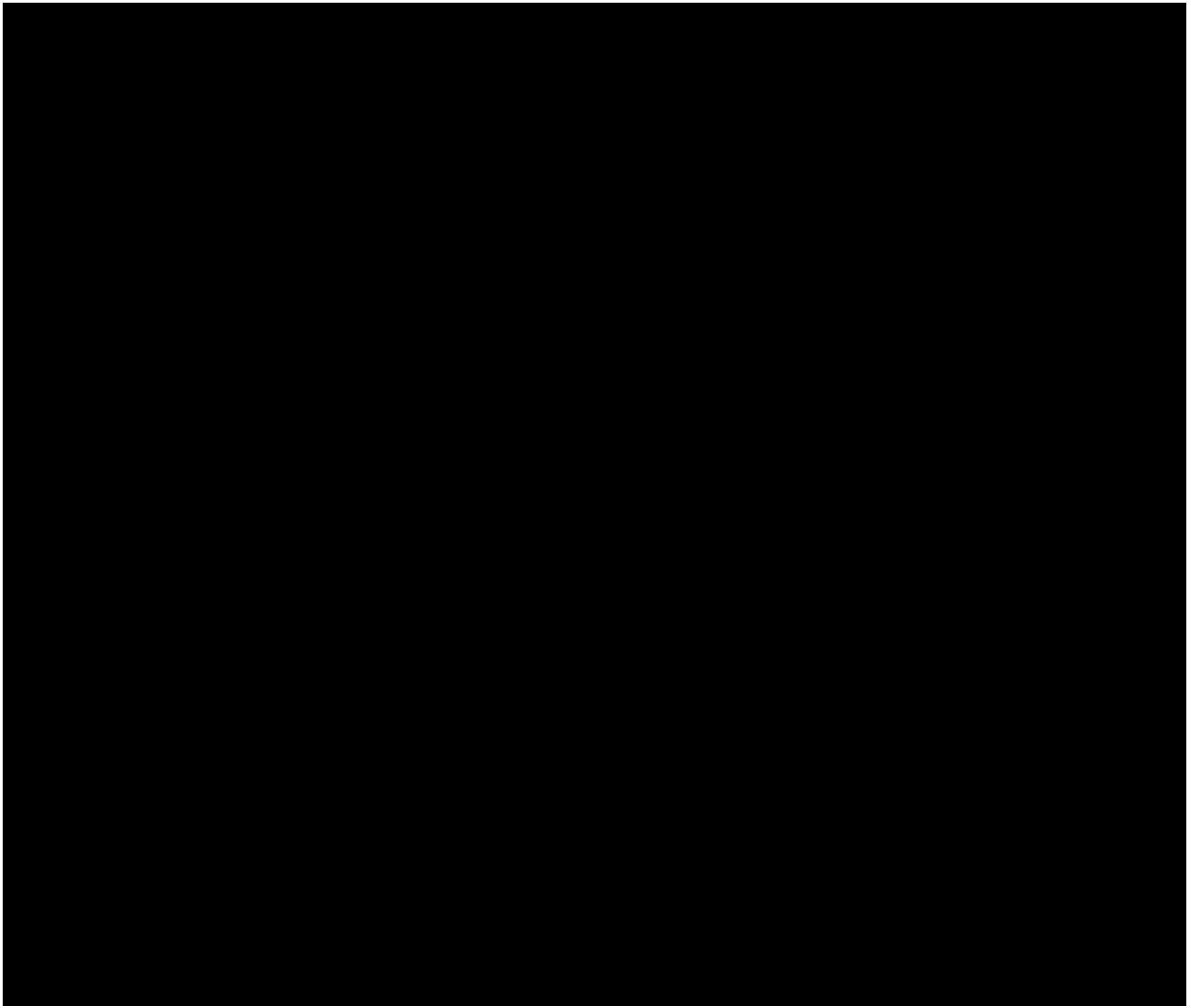
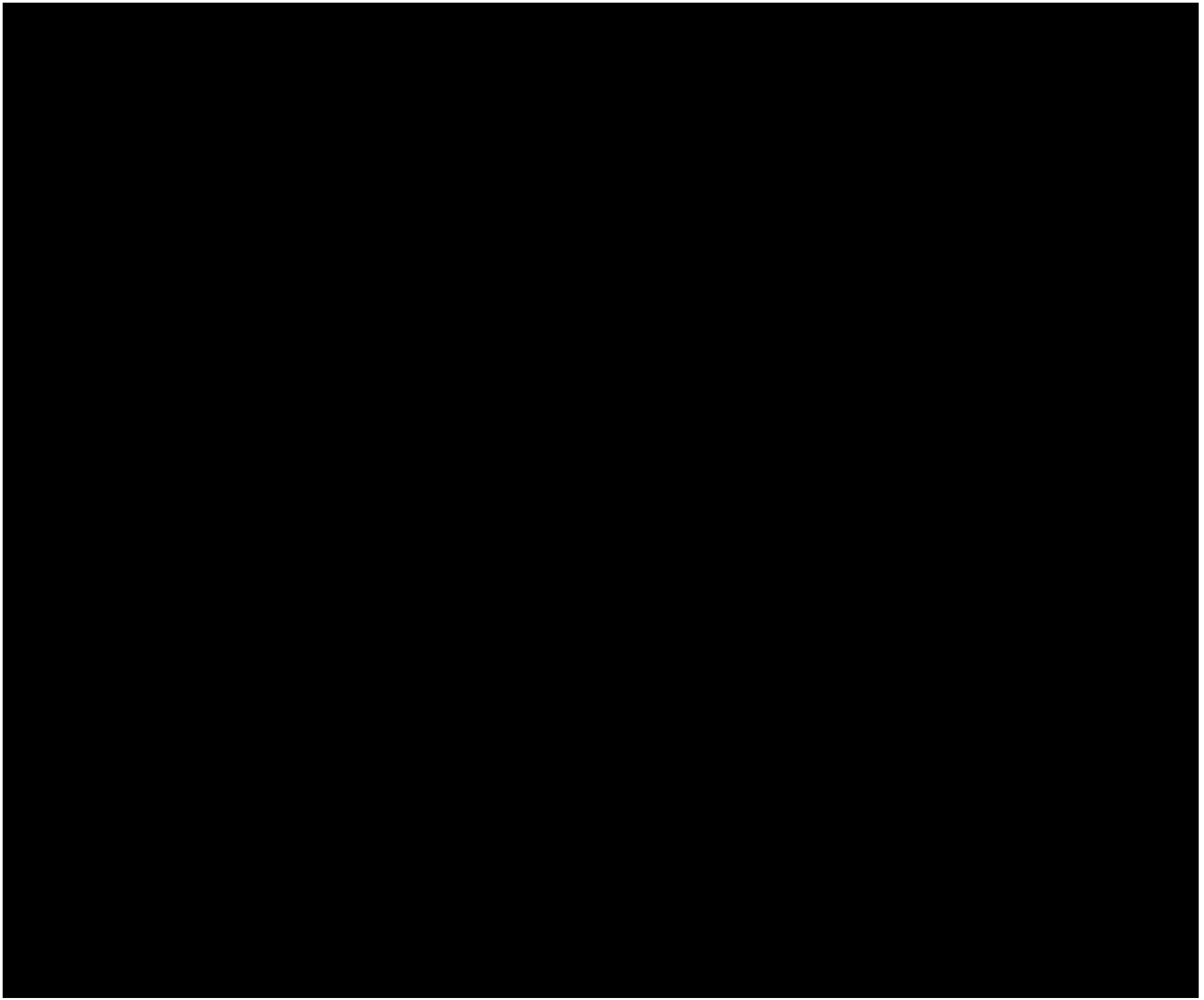
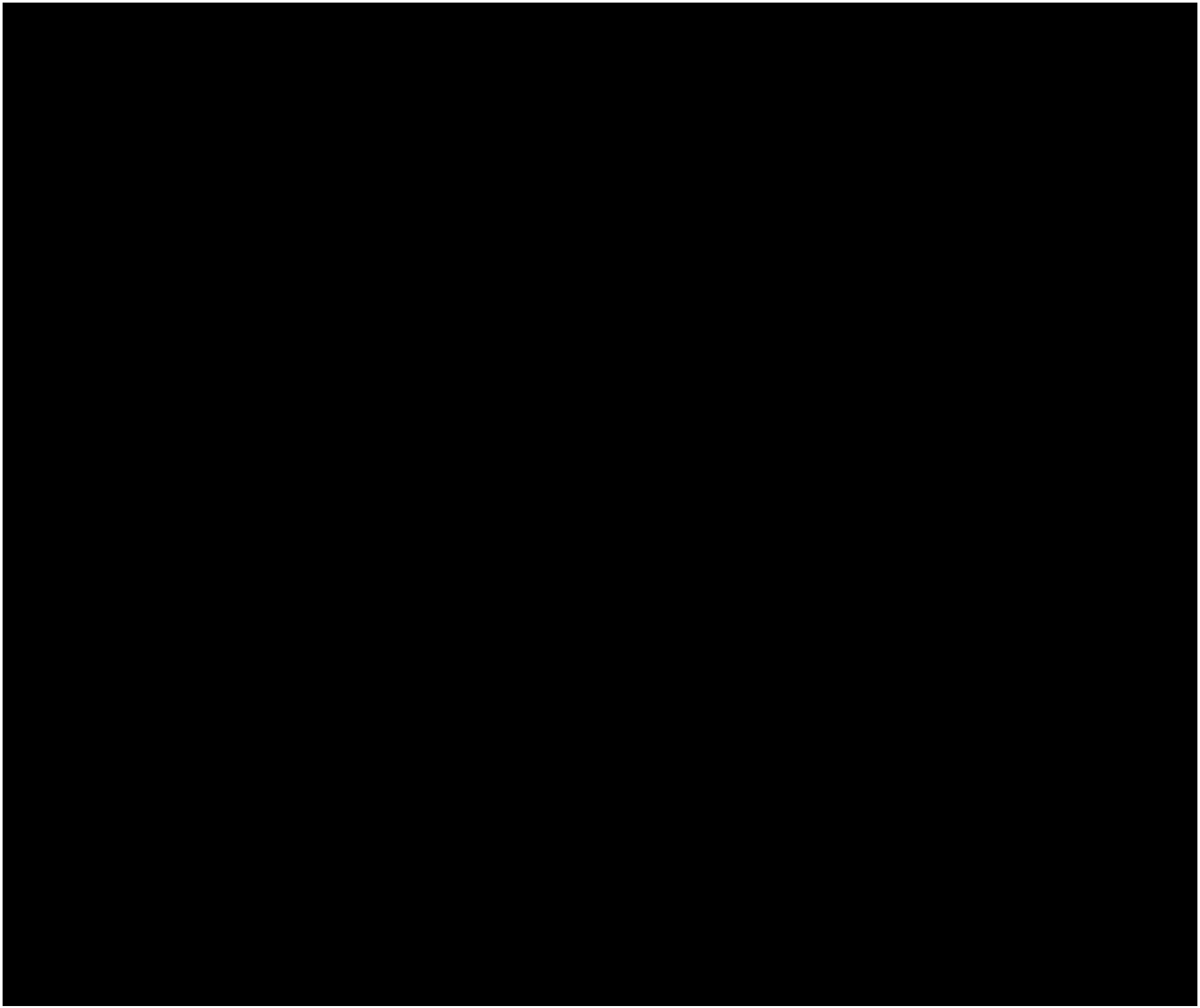
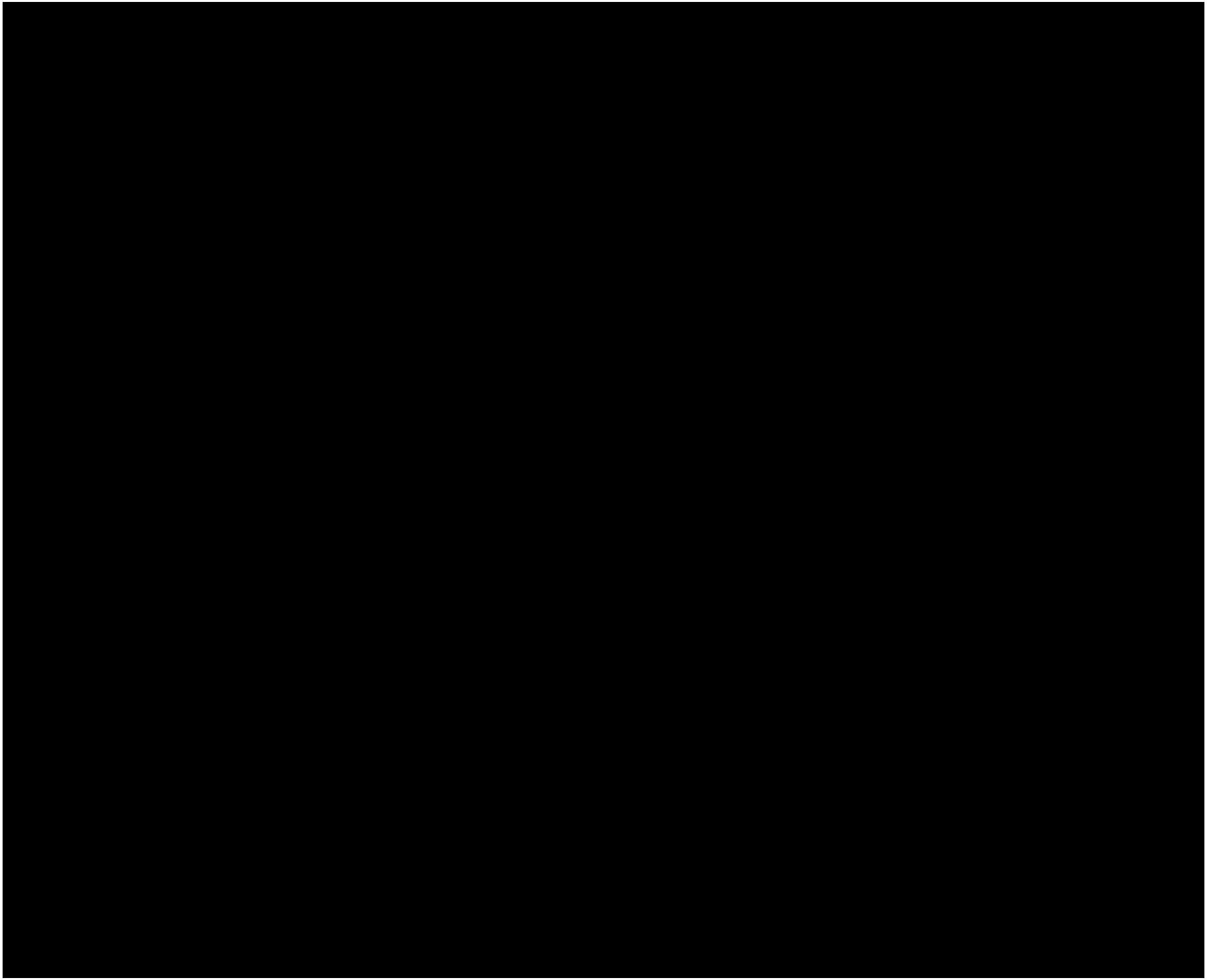
[redacted]









[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

Not applicable.

[redacted]

[redacted]

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

[redacted]