Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Guanfacine (as hydrochloride)

Proprietary Product Name: Intuniv

Sponsor: Shire Australia Pty Ltd

May 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS-IV	Attention Deficit Hyperactivity Disorder – Rating Scale, Version IV
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BP	Blood pressure
bpm	Beats per minute
BPRS-C	Brief Psychiatric Rating Scale for Children
BRIEF	Behavior Rating Inventory of Executive Function
BSFQ	Before-school Functioning Questionnaire (Wil-Hammer)
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement
CGI-P	Connor's Global Index - Parent
CGI-S	Clinical Global Impression – Severity of illness
CHQ	Child Health Questionnaire
CHQ-PF50	Child Health Questionnaire – Parent Form
CHQ-CF87	Child Health Questionnaire – Child Form
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CPRS-R	Connors' Parent Rating Scale – Revised: Short Form
CPRS-R:L	Conners' Parent Rating Scale – Revised: Long Form

Abbreviation	Meaning
CRT	Choice Reaction Time in the Cambridge Neuropsychological Test Automated Battery
CSHQ	Children's Sleep Habits Questionnaire
C-SSRS	Columbia-Suicide Severity Rating Scale
CTRS-R	Connors' Teacher Rating Scale – Revised: Short Form
DAE	Discontinuation due to Adverse Event
DBP	Diastolic Blood Pressure
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision
DSST	Digit Symbol Substitution Task
ECG	Electrocardiogram
FAS	Full Analysis Set
FOCP	Females of Childbearing Potential
GGT	Gamma-glutamyl transferase
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Scale
HCG	Human Chorionic Gonadotropin
HR	Heart rate
HUI2/3	Health Utilities Index – Mark 2 and Mark 3
ICH	International Conference on Harmonisation
ITT	Intention to Treat
IVRS	Interactive Voice Response System
KBIT	Kaufman Brief Intelligence Test
K-SADS-PL	Kiddie-Sads-Present and Lifetime – Diagnostic Interview
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Meaning
MSS	Medication Satisfaction Survey
NDTI	National Disease Therapeutic Index™
NOS	Not otherwise specified
NYPRS-S	New York Parent's Rating Scale – School-aged
ODD	Oppositional Defiant Disorder
PDSS	Pediatric Daytime Sleepiness Scale
PERMP	Permanent Product Measure of Performance
PGA	Parent Global Assessment
PSERS	Pittsburgh Side Effect Rating Scale
PSI/SF	Parent Stress Index – Short Form
PSQ	Post-sleep Questionnaire
PSS	Pictorial Sleepiness Scale
QoL	Quality of Life
QT	QT Interval
QTc	QT Interval Corrected for HR
QTcF	QT Corrected For Heart Rate Using the Fridericia Method
QTcNi	QT Corrected For Heart Rate Using a Subject-Specific Correction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPD503	Intuniv (guanfacine hydrochloride)
SSEQ	Structured Side-Effect Questionnaire

Abbreviation	Meaning
SWM	Spatial Working Memory
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
WFIRS-P	Weiss Functional Impairment Rating Scale - Parent
WBC	White Blood Cell Count

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	22 August 2017
Date of entry onto ARTG	29 August 2017
Active ingredient(s):	Guanfacine (as hydrochloride)
Product name(s):	Intuniv
Sponsor's name and address:	Shire Australia Pty Ltd 225 George Street, Sydney, NSW 2000
Dose form(s):	Modified release tablets
Strength(s):	1 mg, 2 mg, 3 mg and 4 mg
Container(s):	Blister pack
Pack size(s):	Packs of 7 (for the 1 mg and 2 mg strengths only) and 28 tablets
Approved therapeutic use:	*Intuniv is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants). Intuniv must be used as part of a comprehensive ADHD management programme, typically including psychological, educational and social measures*
Route(s) of administration:	Oral (PO)
Dosage:	The recommended starting dose for Intuniv is 1 mg, taken orally once a day, for both monotherapy and when co-administered with psychostimulants.
ARTG number (s):	275313, 275314, 275315 and 275278

Product background

This AusPAR describes the application by Shire Australia Pty Ltd to register a New Chemical Entity product guanfacine (as hydrochloride) 1 mg, 2 mg, 3 mg, and 4 mg modified release tablets on the Australian Register of Therapeutic Goods (ARTG) under the trade name Intuniv for the proposed indication:

> *For the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive).*

The sponsor has proposed a starting dose for Intuniv of 1 mg, taken orally once a day, for both monotherapy and when co-administered with psychostimulants.

The sponsor states that guanfacine hydrochloride is a known active substance to the community [not Australia] and was initially formulated as an immediate release (IR) tablet for the treatment of hypertension. The IR tablet formulation was apparently approved in a number of European Union (EU) member states, under the trade name Estulic, from 1979 to the mid-1980s. The product has subsequently been withdrawn in most member states for commercial reasons and is currently marketed only in Hungary. The sponsor states that it does not belong to the same mother company or group of companies, as the previous marketing authorisation holder of guanfacine hydrochloride. Furthermore, the nonclinical and clinical development of the two products (IR and Modified release (MR)) has been conducted independently by each company without having concluded agreements or exercising concerted practices concerning such development.

Guanfacine modified release tablets are intended to deliver a dose of guanfacine base over the course of 1 day. The dosage form is designed such that the drug is released slowly and therefore is absorbed over an extended period of time, reducing the peak and trough plasma levels associated with multiple daily dosing.

Guanfacine is a selective α2A-adrenergic receptor agonist, which has a 15 to 20 fold higher selectivity for the α2A-adrenergic receptor subtype than the α2B and α2C subtypes. Its mechanism of action in Attention Deficit Hyperactivity Disorder (ADHD) is not known; however, nonclinical data suggests it acts centrally by stimulating post-synaptic α2A-adrenoreceptors located in the locus coeruleus (midbrain) and the prefrontal cortex by modulating the levels of norepinephrine. Importantly, these regions are known to play a major role in attention, organisation and planning, along with impulse control. Deficits in these domains are implicated in the symptoms associated with ADHD. Guanfacine is not a central nervous system stimulant.

Regulatory status

This is a new chemical entity for Australian regulatory purposes.

Guanfacine was approved in the EU on 17 September 2015 for the indication:

> *Intuniv is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Intuniv must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures.*

Guanfacine was approved in the USA on 2 September 2009 for the indication:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications.*

Guanfacine was also approved in Canada on 8 September 2015:

> *Intuniv XR (guanfacine hydrochloride extended-release tablets) is indicated as monotherapy for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents aged 6 to 17 years. Intuniv XR is also indicated as adjunctive therapy to psychostimulants for the treatment of ADHD in children and adolescents, aged 6 to 17 years, with a sub-optimal response to psychostimulants.*

An application for registration was lodged in Switzerland on 27 November 2015 and is pending.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

II. Registration timeline

Table 1: Registration timeline for Submission PM-2016-00711-1-1

Description	Date
Submission dossier accepted and 1st round evaluation commenced	31 May 2016
1st round evaluation completed	23 December 2016
Sponsor provides responses on questions raised in 1st round evaluation	23 February 2017
2nd round evaluation completed	4 April 2017
Request for Advisory Committee advice and/or Delegate's Overview	1 May 2017
Sponsor's response to Delegate's Overview	11 May 2017
Advisory Committee meeting	2 June 2017
Registration decision	22 August 2017
Entry onto ARTG	29 August 2017
Number of TGA working days from commencement of evaluation to registration decision *	233

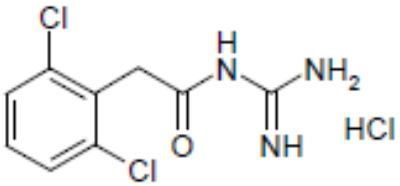
* Target timeframe for standard applications: 220 working days. Statutory timeframe: 255 working days.

III. Quality findings

Drug substance (active ingredient)

The drug substance *guanfacine hydrochloride* is selective α_2-adrenergic receptor agonist. It is manufactured by chemical synthesis. It is achiral and is obtained as a single structural isomer. Its chemical structure is shown in Figure 1 below.

Figure 1: Guanfacine hydrochloride



Intuniv is a crystalline powder. It is sparingly soluble in water and pH 7.0 buffer slightly soluble in pH 2.0, pH 4.0 and pH 9.0 buffers, soluble in methanol, slightly soluble in acetone and insoluble in isopropanol and ethyl acetate. It has a pKa of 7.69, and a partition coefficient of 0.10.

Guanfacine hydrochloride is sourced from two drug substance manufacturers.

- The drug substance specification imposed by the finished product manufacturer for analysis of guanfacine hydrochloride from both manufacturers includes appropriate tests and limits, including acceptable particle size limits which were appropriately set based on tablet batches used in pivotal studies.
- Several polymorphic forms are reported in the literature. The synthetic route followed by each manufacturer afforded only one polymorphic form, and the same polymorphic form of the drug substance was obtained from both sites.

Drug product

The drug product is modified release tablet containing guanfacine (as hydrochloride) 1 mg, 2 mg, 3 m or 4 mg as the active ingredient. The different strengths are distinguished by different colour and shapes. Each strength tablet is marked '503' on one side and the strength on the other side.

All strengths are packaged in blisters in packs of 7 (for the 1 mg and 2 mg strengths only) and 28 tablets.

Formulation

The proposed modified tablets contain *hypromellose* as the conventional rate-release controlling excipient. The different strengths were manufactured using two different tablet blends, namely: Blend A (for 1 mg and 2 mg) and Blend B (for 3 mg and 4 mg), followed compression.

There is no difference between the formulations used in pivotal clinical batches and the formulation proposed for registration.

Manufacturing process

The proposed modified tablets are manufactured by Dry Bending, followed by Direct Compression.

A modified process was proposed for commercial manufacturing and was validated with production scale batches of each strength.

The Phase III clinical batches were manufactured at a different site and by a different manufacturing process to that proposed; however, the bridging Study 503-120 concluded that the tablet manufactured by different processes are bioequivalent.

Control of finished product

The proposed modified release tablet is adequately controlled by acceptable release and shelf-life specifications. All issues that were raised regarding the tests and limits of each specification parameters have been adequately addressed.

Stability:

Stability data have been generated under accelerated and long-term conditions. The results showed that the finished product is relatively stable under both storage conditions. A shelf-life of 48 months stored below 25°C has been assigned for all strengths of the proposed product when packaged in the proposed blister pack.

Biopharmaceutics

Several biopharmacetic studies were provided in support of this submission. The following studies were evaluated (see Table 2):

Study number	Study type		
Study SPD503-104 (food effect & relative bioavailability)	Food effect (single 4 mg) Relative bioavailability (1 x4 mg vs 4 x 1 mg)	Full evaluation	Food increased C_{max} and AUC by 75% and 38%, respectively.
Study503-109 (dose proportional) (relative bioequivalence of 2 mg and 4 mg at initial development site versus initial commercial manufacturing site	Dose proportional 1, 2, 4 mg tablet formulation. BE of SPD503 tablets manufactured at the initial development site and initial commercial manufacturing site following single doses of 2 and 4mg, respectively.	Full evaluation	The investigators concluded that tablets manufactured at the two sites were bioequivalent and that exposure from the three strengths was dose-proportional.
SPD503-120 (relative bioequivalence of 4 mg at initial commercial manufacturing site versus current commercial manufacturing site	To assess the bioequivalence of 4mg SPD503 tablets manufactured at the 2 different sites following a single dose of SPD503.	Full evaluation	The investigators concluded that tablets manufactured at the two sites were bioequivalent.

Study number	Study type		
SPD503-203 (steady state 1 mg and 4 mg)	Phase II PK profile of SPD503 after a 1mg single dose and multiple dosing of 1 and 4 mg/day, in paediatric patients.	Summary	

The results of the biostudies provided support the conclusions that:

- Food has a significant effect on the pharmacokinetics of guanfacine, with administration after a high-fat meal increasing peak plasma concentration (C_{max}) by 75% and area under the plasma concentration versus time curve (AUC) by 38%, and
- 1 x 4 mg tablet is bioequivalent to 4 x 1 mg tablets,
- The tablets manufactured at the [information redacted] site are bioequivalent to the same strength tablets manufactured at the [information redacted] site, and
- The pharmacokinetics of guanfacine are reasonably linear over doses ranging from 1 mg to 4 mg (although the 90% confidence interval (CI) for the C_{max} ratio between the 1 mg and 2 mg strengths was not completely contained within the 80-125% range), and
- The tablets manufactured with the modified manufacturing process and with the former manufacturing process sites are bioequivalent.

Quality summary and conclusions

Approval for registration of the proposed product can be recommended from a pharmaceutical chemistry and biopharmaceutic perspective.

IV. Nonclinical findings

Introduction

General comments

The recommended maintenance dose range of Intuniv is 0.05–0.12 mg/kg/day (total daily dose between 1–7 mg). Doses > 4 mg/day have not been evaluated in children (6–12 years) and doses > 7 mg/day have not been evaluated in adolescents (13–17 years).

Guanfacine was originally developed by Sandoz AG as an anti-hypertensive agent. It was registered in the USA in 1986 as Tenex, an immediate-release form, for the treatment of hypertension. An extended-release formulation of guanfacine (Intuniv) was developed by the sponsor and was approved by the FDA in 2009 for the treatment of paediatric ADHD.

The data reviewed for this assessment of Intuniv came from four sources: literature reports of clinical and non-clinical studies performed using guanfacine (usually in rapid-release form); the FDA review (dated 20 December 1985) of Sandoz AG studies performed in support of Tenex; the FDA review (dated 20 June 2007), of studies performed in support of the registration of Intuniv, and an addendum (dated July 2009) on drug-induced cardiac valvulopathy; and newer studies (performed in response to deficiencies noted by other

drug regulators) provided by the sponsor. Much of the primary data on guanfacine has not been sighted by the nonclinical evaluator.

Because many of the studies referenced in this assessment date from the 1970s, 1980s, and 1990s, they were not performed to Good Laboratory Practice (GLP) standards.

Pharmacology

ADHD is a common neurobehavioural problem that can afflict children, adolescents, and adults. The condition is characterised by inattentive, hyperactive, and impulsive behaviour. Various studies suggest that ADHD has a high level of heritability, however, the aetiology and causative genes remain unclear or controversial. Thought processes that regulate behaviours such as attention and emotions are held in the working memory and are dependent on the activity of networks of glutamatergic pyramidal neurons in layer III of the dorsolateral prefrontal cortex (PFC) that generate persistent firing in the absence of sensory stimulation. Dysfunction of these neuron networks has been implicated in ADHD.

Persistent neuron firing in the PFC is thought to be based on the activation of glutamate receptors (probably either N-methyl-D-aspartate (NMDA) or metabotropic glutamate receptors) on post-synaptic spines resulting, directly or indirectly, in a rapid, highly localised increase in the free calcium (Ca^{2+}) ion concentration that initiates signalling pathways within dendrites. Glutamatergic signalling in the PFC is regulated by neurons that release neurotransmitters such as acetylcholine, gamma-Aminobutyric acid (GABA), and the catecholamines dopamine and noradrenaline, which can bind receptors located on dendritic spines. Noradrenaline can interact with the members of three families of metabotropic (G protein coupled) adrenergic (Ad) receptors: α1 (consisting of α1A, α1B, and α1D), α2 (consisting of α2A, α2B, and α2C) and β (consisting of β1, β2, and β3). The α2-Ad receptors show the highest affinity for noradrenaline and in monkey PFC were almost exclusively of the α2A type. α2-Ad receptors couple with $G\alpha_i$ protein and their activation results in the inhibition of adenylyl cyclases (AC) and the consequent decrease in intracellular cAMP production. The α2A-Ad receptor agonist, guanfacine, has been shown to improve working memory performance when infused into monkey PFC. Conversely, the α2-Ad receptor antagonist, yohimbine, impaired working memory performance in monkeys. Such effects of Ad receptor agonists and antagonists on PFC function are not readily explained based on the biochemical pathways that are usually described as being activated or inhibited by these receptors. For example, the activation of α2-Ad or β2-Ad receptors can improve PFC function despite having apparently opposite effects on cAMP production, and the activation of α2-Ad receptors can lead to the inhibition of signalling from NMDA receptors.

A possible explanation for the ability of α2-Ad receptor activation to improve PFC function derives from the finding of defined composition macromolecular signalling complexes that occupy distinct microdomains within the dendritic spine. Tight coupling (for example due to the short lifetime of signalling intermediates) between receptors and their macromolecular complexes means that the signal produced following agonist binding is largely a reflection of the identity of the associated signalling proteins.

The hyperpolarisation-activated cyclic nucleotide-gated (HCN) cation channels are permeable to sodium (Na^+) and potassium (K^+) ions and are opened by 3'5'-cyclic adenosine monophosphate (cAMP) binding. They are found at the base of dendritic spines in monkey PFC and act to depolarise the membrane and dampen dendritic excitability. In this way, HCN channels are thought to act as gatekeepers, determining whether or not signals from individual dendritic spines are allowed to enter the pyramidal cell microcircuit. HCN channels have been shown to co-localise with α2A-Ad receptors in monkey PFC. Accordingly, α2A-Ad receptor agonists such as guanfacine may act, via

localised inhibition of cAMP production, to enhance dendritic signalling by inhibiting HCN channels.

Primary pharmacology

In vitro studies have demonstrated that guanfacine is an agonist that shows selectivity and moderately strong binding affinity (K_i = 13.3 nM) for human recombinant α2A-Ad receptor.

Studies using the spontaneously hypertensive rat (a model for ADHD) have shown that dosing with guanfacine can improve ADHD related behaviours. Using the blood-oxygen-level dependent (BOLD) contrast imaging technique, it was shown that such improvement correlated with positive BOLD effects (thought to reflect increased neuronal activity) in frontal regions of the rat brain, including the PFC, and negative BOLD effects in brain regions associated with motor activity.

Secondary pharmacodynamics and safety pharmacology

The sponsor's studies of ADHD patients given a maximal dose of 4.0 mg (base equivalent) of guanfacine hydrochloride indicated a plasma C_{max} of 41 nM and a mean plasma steady state concentration of 27 nM. Assuming plasma protein binding of approximately 70%, the unbound C_{max} would be approximately 12 nM. The maximum luminal concentration (assuming complete dissolution in 250 mL[1]) would be 65 μM, but would be much lower for an extended-release formulation such as Intuniv.

Guanfacine hydrochloride was tested for binding to a panel of various proteins; primarily neurotransmitter receptors. At concentrations up to 100 nM, guanfacine only showed significant binding to the α2A-Ad receptor, whilst at the non-clinically relevant concentration of 10 μM, it showed binding to several other receptors and transporters, including α2B- and α2C-Ad receptors, serotonin receptors and imidazoline receptors. The agonist activity of guanfacine at the α2A-, α2B- and α2C-Ad receptors was compared with clonidine, another adrenergic receptor agonist that has been used to treat ADHD. Whilst guanfacine showed specificity for activation of α2A-Ad receptors (being approximately 7 and approximately 10 fold less active at α2B- and α2C-Ad receptors, respectively), clonidine showed comparable activity at α2A- and α2B-Ad receptors.

Because of concerns that guanfacine may be a serotonin receptor 2B subtype (5-HT_{2B}) receptor agonist and thereby act as a valvulopathogen in patients (see details below under *Repeat-dose toxicity*), its affinity for and ability to activate the human 5-HT_{2B} receptor were quantified in more recent studies. In competitive binding assays, guanfacine showed approximately 100-fold higher affinity for the α2A-Ad receptor as compared to the 5-HT_{2B} receptor (50% inhibitory concentration (IC_{50}) values of < 3.0 x 10^{-9} and 3.5 x 10^{-7} M, respectively) and showed approximately 30 fold lower affinity for the 5-HT_{2B} receptor than serotonin (IC_{50} values of 93.5 nM for serotonin and 2.8 μM for guanfacine). In a functional assay, guanfacine was approximately 1000 fold less effective than serotonin at activating 5-HT_{2B} receptors (50% effective concentration (EC_{50}) = 4.1 x 10^{-8} and 4.5 x 10^{-11} M, respectively). At expected plasma concentrations in patients (see above) guanfacine would not be expected to show significant binding to or activation of 5-HT_{2B} receptors.

Safety pharmacology studies examined several systems:

Cardiovascular: In telemetered dogs, dosing at 0.5 or 1.5 mg/kg did not have a significant effect on arterial blood pressure (BP) or electrocardiogram (ECG) parameters, but did produce a pronounced and prolonged bradycardia, an effect seen in other animal studies.

[1] Guideline on the Investigation of Drug Interactions', EMA, 21 June 2012

The apparent lack of effect on ECG parameters, however, contrasts with the findings of a 1 year repeat-dose toxicity study (see below), in which dogs dosed at 1 or 3 mg/kg/day showed significant prolongation of the QT interval[2] and a dose related increase in the incidence and intensity of notched T-wave. The sponsor has argued, however, that the latter results should be tempered by the fact that: '*QT interval was not corrected for heart rate in this study, and so the observed prolongation was confounded by reduced heart rate*.' Whole cell patch clamp recording of hERG transfected human embryonic kidney cells (HEK293) cells perfused with balanced salt solution (BSS) containing guanfacine hydrochloride at a concentration of 1 µg/ml (approximately 4 µM) showed no effect of the test article on the tail current. Accordingly, clinical use of guanfacine might be expected to produce bradycardia but not QT-interval prolongation.

Excretory: Guanfacine has been shown to inhibit faecal excretion in mice, consistent with the known ability of α2A-Ad receptor activation to inhibit neurogenic contraction of the GI tract via inhibition of the release of acetylcholine. Such effects may be related to the gastrointestinal (GI) tract associated adverse events that are commonly noted in patients taking guanfacine (sponsor's Clinical Overview). Studies in dogs and rats showed that guanfacine could increase urine flow and sodium excretion but it is difficult to determine whether these findings have clinical relevance.

Respiratory: Contradictory effects of guanfacine on respiration have been noted in animal studies (the sponsor's Pharmacology Written Summary). Deaths of mice and rats occurring soon after guanfacine administration were attributed to respiratory paralysis. Guanfacine was also shown to produce transient respiratory depression in rabbits but produced stimulation of respiration in goats. The lack of pharmacokinetic data for such studies makes it difficult to assess their relevance to human treatment.

A pharmacodynamic interaction study showed that although guanfacine and D-amphetamine could improve ADHD related behaviours in spontaneously hypertensive (model of ADHD) and control rats, the effects were not consistently additive and a combination of sub-effective doses of the two drugs did not produce improvement.

Pharmacokinetics

Radiolabelled guanfacine hydrochloride showed rapid absorption following oral dosing of rats, dogs, and monkeys, with time to peak C_{max} (T_{max}) for radioactivity in plasma occurring at 0.5 to 2 h post dosing. Uptake of immediate-release forms of guanfacine hydrochloride was similarly rapid in humans, with T_{max} occurring at approximately 2–3 h post dosing. T_{max} in adult humans for Intuniv tablets, which are an extended-release formulation of guanfacine, was at approximately 6 h. Based on the levels of excretion in urine (see below), the bioavailability of guanfacine hydrochloride appears to be high in humans (> 80%) and various animal species. Studies using juvenile rats suggested that C_{max} and AUC values generally increased in a more-than-dose-proportional manner over the range 0.3–3 mg/kg/day. However, the sponsor's studies suggested that C_{max} and AUC values increased approximately dose-proportionally in children and adolescents with ADHD. The little data available regarding the plasma terminal half-life ($t_{½}$) value for orally administered guanfacine in animals suggests a value of approximately 2–5 h in rats. In contrast, both studies presented by the sponsor and literature studies indicate plasma terminal $t_{½}$ values for children and adult humans in the range 13 to 23 h, suggesting that guanfacine elimination is much slower in humans than in rats.

[2] The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarisation and repolarisation of the ventricles. A prolonged QT interval is a marker for potential ventricular tachyarrhythmias like Torsades de pointes and a risk factor for sudden death.

Limited data, for humans only, suggested a moderate level of binding (approximately 70%) of guanfacine to plasma protein that was not influenced by test article concentration or dosing route. Studies of the permeability of guanfacine across Caco-2 cell monolayers suggested that guanfacine is a highly permeable compound. The volume of distribution for guanfacine in man was estimated at 6.5 L/kg; a relatively high value that suggests significant uptake of guanfacine by tissues. When uptake of radioactivity into rat tissues was measured after oral dosing with radiolabelled guanfacine, the highest levels of radioactivity were found in liver and kidney, whilst brain (target organ) and testis showed the lowest values. However, parental drug (as opposed to metabolites) was shown to be the major radioactive material in rat brain. There was no evidence for accumulation of radioactivity in any tissue.

The metabolism of guanfacine primarily features modifications to the phenyl moiety, typically starting with hydroxylation(s) or hydration, often followed by glucuronidation or sulfation. Various metabolites were identified in the plasma of rats (13 metabolites), dogs (14), and cynomolgus monkeys (17); however, most were present at low levels. A comprehensive identification and quantification of the human metabolites does not appear to have been performed, although it is stated that 3-hydroxy guanfacine and its glucuronide and sulfate conjugates are the major metabolites found in human plasma. The major circulating metabolites in animal species were dihydro-diol guanfacine (dog) and sulfate conjugates of hydroxy guanfacine (rat, dog, and cynomolgus monkey). Hence, there is only a partial overlap between the major circulating metabolites found in rat and dog (the species used for repeat-dose toxicity studies) and in man. At T_{max} in rats and dogs dosed orally with radiolabelled guanfacine, parental drug represented 4.4% and approximately 7–8%, respectively, of the radioactivity in plasma. Similarly, parental drug comprised 7.5% of $AUC_{0-24\,h}$ for total radioactivity in plasma of cynomolgus monkeys. Comparable data on the fraction of dose as parental drug in plasma could not be found for humans, however, based on the slower elimination kinetics, it is likely that levels are higher than in animals. In vitro reactions using human, recombinant CYPs indicated that CYP3A4 and, to lesser extents, CYP2C19 and CYP2D6 can metabolise guanfacine. Consistent with that finding, exposure to guanfacine in healthy humans was significantly increased by co-administration with ketoconazole (a selective inhibitor of CYP3A4).

Following oral dosing of rats with radiolabelled guanfacine, radioactivity was collected in both faeces (56% of total) and urine (37%). Results from bile duct-cannulated rats showed that essentially all faecal radioactivity came from bile and that there was a significant level of enterohepatic circulation. In both dogs and cynomolgus monkeys, radiolabelled material was predominantly excreted in urine (77% and 61%, respectively, in urine as compared to 3% and 6%, respectively, in faeces). A comprehensive mass-balance study for guanfacine dosing of humans does not appear to have been published, however, 82% of total radiolabel was collected in urine within 4 days of oral dosing of aged, hypertensive patients.

Rats and, to a lesser extent, mice have been the species primarily used to explore toxicity issues associated with guanfacine hydrochloride. Pharmacokinetic (and other) results suggest, however, that these species are likely a poor base for extrapolation to humans.

Pharmacokinetic drug interactions

P-gp: Guanfacine showed similar permeability in both apical-to-basolateral and basolateral-to-apical directions across Caco-2 cell monolayers and, at concentrations up to 40 μM, it had no effect on the transport of paclitaxel (a P-gp substrate). These results suggest that guanfacine permeation of Caco-2 cell monolayers is primarily a passive process, and that guanfacine is not a substrate of P-gp and would not be expected to interfere with the transport of P-gp substrates.

Cytochrome P450 (CYP) isozyme effects: Incubation of pooled human hepatic microsomes with guanfacine at up to 3.5 μM did not produce reversible inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 enzymic activity. Similarly, pre-incubation for 15 min with guanfacine did not produce irreversible inhibition of the same enzymic activities. Such results suggest that plasma levels of guanfacine are unlikely to influence hepatic CYP metabolism but do not exclude the possibility of effects on intestinal metabolism. In a similar study, using pooled human hepatic microsomes, guanfacine at 10 μM produced approximately 30% inhibition of CYP2C8 enzymic activity but had no effect at the concentrations found in patient plasma. Pre-incubation with guanfacine for up to 30 min also had no effect on CYP2C8 enzymic activity. Guanfacine at up to 100 μM was also tested for potential to inhibit CYP2B6 enzymic activity in pooled human liver microsomes and CYP3A activity in pooled human intestinal microsomes. The IC_{50} values for CYP2B6 and CYP3A were approximately 100 μM and 29 μM, respectively. Comparison with circulating and intestinal lumen concentrations of guanfacine (see above) suggests that guanfacine would not affect these CYP activities in patients.

Because of concerns that a 15 min pre-incubation with guanfacine was too short to exclude possible time dependent inhibition, the above study was repeated using pre-incubation of human liver microsomes for 30 min with guanfacine concentrations up to 100 μM. Such conditions had little or no effect on the guanfacine IC_{50} values for CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A, suggesting that guanfacine hydrochloride is unlikely to be a time dependent inhibitor of these enzymes. CYP induction was tested by incubating human hepatocytes from 3 separate donors with guanfacine hydrochloride at up to 0.815 μM for CYP1A2 and CYP2B6 or at up to 6.5 μM for CYP3A. After 72 h of incubation in the presence of guanfacine, cultures were assayed for enzymic activity and for mRNA level. Neither assay suggested that guanfacine, at concentrations much higher than found in patients, is likely to induce CYP1A2, CYP2B6 or CYP3A.

Transporters: Studies using monolayers of transporter-transfected cell lines or inverted vesicles showed that guanfacine is not a substrate of Breast Cancer Resistance. Protein (BCRP), organic anion transporting polypeptide 1B1 (OATP1B1/B3), OAT1/3, or MATE1/2-K, but is a low affinity substrate of Organic Cation Transporter 1 (OCT1) (K_m = 11.2 μM) and of OCT2 (K_m = 4.5 μM). Similarly, guanfacine showed little or no inhibition of substrate transport by BCRP (maximum guanfacine concentration tested = 6.5 μM), OATP1B1/B3 (8 μM), OAT1/3 (0.82 μM), OCT2 (0.82 μM), multidrug and toxin extrusion protein 1 (MATE1) and 2-K (MATE1/2-K) (0.82 μM), BSEP (8.2 μM), or MRP2 (8.2 μM). Guanfacine showed weak inhibition of OCT1 (47% inhibition at 8 μM). Such inhibition is not expected to be clinically relevant.

Uridine 5'-diphospho-glucuronosyltransferase (UGT): Neither guanfacine nor 3-hydroxy guanfacine, over the concentration range 0.04 to 10 μM, produced significant inhibition of the activities of UGT1A1, 1A4, 1A6, 1A9 or 2B7.

Toxicology

Acute toxicity

Guanfacine showed high toxicity in mice when given either intravenously (IV) or orally (50% lethal dose (LD_{50})(oral): males = 16 mg/kg; females = 50 mg/kg; maximum non-lethal dose (oral): males = 3 mg/kg and females = 5 mg/kg). However, guanfacine showed more moderate toxicity in rats (LD_{50} (oral): males = 610 mg/kg; females = 210 mg/kg; maximum non-lethal dose (oral): males = 255 mg/kg and females = 100 mg/kg). Clinical signs were generally similar in both species and likely reflected exaggerated pharmacology, and included corneal opacity, respiratory depression, decreased locomotor

activity, ataxic gait, exophthalmos, mydriasis, piloerection, and cyanosis. Deaths occurring soon after test article administration were attributed to respiratory paralysis.

Repeat-dose toxicity

Repeat-dose toxicity studies used mice, rats, and dogs, and derived from different sources (scientific literature, FDA assessment of Tenex (1986), and sponsor's reports). Many of the studies are quite old and only one was conducted in compliance with GLP standards. In addition to questions about the usefulness of rodents as models for human response to guanfacine, it should be noted that most of the rodent studies used dietary administration of test article (see Table 3). This could be a further complication in extrapolating rodent results to humans. The results of the sponsor's studies examining repeat-dose toxicity in juvenile rats are examined separately under 'Paediatric use' (see below).

The association between the use of some drugs, such as the anorexigen fenfluramine and certain ergots, and the induction of cardiac disease has been attributed to the activation of the 5-HT_{2B} receptor leading to mitogenic activity of fibroblasts in the heart valves.[3] In vitro screening of around 2,200 approved or investigational medications identified 27 that had agonistic activity at the 5-HT_{2B} receptor, including 7 known valvulopathogens.[4] The 27 5-HT_{2B} receptor-agonists also included guanfacine. This finding raised concerns that long-term use of guanfacine could be associated with a significantly increased risk of cardiac disease. The data of Huang *et al*. (2009) showed, however, that in most assays of 5-HT_{2B} receptor activation guanfacine had significantly lower potency than the known valvulopathogens. For example, in an assay of agonist-induced proliferation of a cell line expressing 5-HT_{2B} receptors, most known valvulopathogens produced a significant increase in proliferation at 1 nM, whereas 30 nM guanfacine was required to produce a significant increase. The results of the sponsor's studies examining whether guanfacine acts as a valvulopathogen in rodents are discussed below.

Relative exposure

Exposure ratios for guanfacine were calculated based on conversion of dose to mg/m^2 and, in the case of the two repeat-dose toxicity studies for which TK values were available, by comparison with a plasma AUC_{0-24h} value for paediatric, ADHD patients from Clinical Study SPD503-107 (see Table 3). The values obtained suggest low to modest exposure margins between the animal experiments and patient exposure. For a few studies, the exposure ratios achieved at the No observable adverse effect level (NOAEL) dose are bolded in Table 3. As indicated by the two studies where exposure ratios calculated by the two methods could be compared, the mg/m^2-derived values likely exaggerate the true exposure ratio (the exposure ratios based on body surface area (BSA) were about 1.6 to 13 times that based on AUC). This could partly reflect a higher rate of guanfacine metabolism in rodents as compared to humans.

Major toxicities

A consistent finding from the studies with rats and dogs was an association between guanfacine dosing and failure to gain or loss of weight. At least for rats, these findings occurred at drug exposure levels that were likely comparable with clinical levels. In contrast, guanfacine dosing has been associated with decreased weight loss in steers[5] and

[3] Hutcheson J.D., Setola V., Roth B.L. and Merryman W.D. (2011) Serotonin receptors and heart valve disease – it was meant 2B. Pharmacology and Therapeutics, 132: 146–157.
[4] Huang X.P., Setola V., Yadav P.N., Allen J.A. et al. (2009) Parallel functional activity profiling reveals valvulopathogens are potent 5-hydroxytryptamine2B receptor agonists: implications for drug safety assessment. Molecular Pharmacology, 76: 710–722.
[5] Hunter R. A. (1992) The effect of the α2-adrenergic agonist, guanfacin, on the energy metabolism of steers fed on low-quality-roughage diets. British Journal of Nutrition, 67: 337–343.

excessive weight gain in children (see below). Glucosuria has been reported as an acute finding in rats dosed subcutaneously (SC) with guanfacine hydrochloride at 0·5 mg/kg[6] and rats dosed orally at 30 mg/kg/day for 5 weeks showed a significant elevation of blood glucose level. Similarly, dogs dosed orally at 3 or 10 mg/kg/day showed marked increases in blood sugar levels at 2 h after dosing. This effect appeared to ameliorate such that dogs showed decreased glucose levels after lengthy periods of dosing. The induction of hyperglycaemia by guanfacine appears consistent with the finding that activation of α2A-Ad receptors on rodent pancreatic islet β cells directly inhibits the release of insulin.[7] Hyperglycaemia could be responsible for the guanfacine-induced weight loss seen in rodents. However, the sponsor notes in the sponsor's Clinical Overview- Addendum that there was no indication from long-term patient studies for guanfacine induced increases of blood glucose.

Species	Study duration [Study no.]	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	mg/m² [b]	Exposure ratio[a]	
					AUC_{0-24h}	mg/m²
Mouse (OF1)	78 weeks [carcinogenicity]	1.0, 3.0, 10.0 (diet)	–[c]	3, 9, 30	–	0.9, 2.7, 9.1
Rat (JCL-SD)	5 weeks [Nakajima *et al*. 1980]	0.3, **1**, **3**, 10, 30; 6 days per week (PO gavage)	–	1.5, **5.1**, **15**, 51, 154 [d]	–	0.5, **1.6**, **4.6**, 16, 47
Rat (OFA)	102 weeks [carcinogenicity]	♂ = 0.49, 1.37, 5.0; ♀ = 0.60, 1.65, 6.19 (diet)	–	2.9, 8.2, 30 3.6, 9.9, 37.1	–	0.9, 2.5, 9.1 1.1, 3.0, 11
Rat (OFA)	4 weeks [impurities; R01020-SPD503]	**10** (diet)	–	**60**	–	**18**
Rat (Harlan	≤94 days	3, 10 (diet)	70.8,	18,	0.4,	5.4,

[6] Gazzola C. and Spiers W.G. (2002) Effects of the α2-adrenoceptor agonist, guanfacine, on growth rate, glucose, corticosterone, insulin and energy partitioning in rats. Animal Science, 74: 455–459.
[7] Angel I., Niddam R. and Langer S.Z. (1990) Involvement of alpha-2 adrenergic receptor subtypes in hyperglycemia. Journal of Pharmacology and Experimental Therapeutics, 254: 877–882.
Hsu W.H., Xiang H.D., Rajan A.S. and Boyd A.E. III (1991) Activation of α2-adrenergic receptors decreases Ca2+ influx to inhibit insulin secretion in a hamster β-cell line: an action mediated by a guanosine triphosphate-binding protein. Endocrinology, 128: 958–964

Species	Study duration [Study no.]	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	mg/m^2 [b]	Exposure ratio[a]	
					AUC_{0-24h}	mg/m^2
SD; ♂)	[cardiac valvulopathy; R3343M-SPD503]		213	60	1.3	18
Rat (HsdHan:WIST; ♂)	5 or 10 days [repeat-dose toxicity; R3666M-SPD503]	7.5 (5 days), 2 x 7.5 (5 days), 2 x 7.5 (4 days) and then 2 x 10 (6 days) (PO (gavage))	397, 599, 3500	45, 90, 120	2.4, 3.7, 22	14, 27, 36
Dog (beagle)	90 days [repeat-dose toxicity]	**1.0**, 3.0, 5/10	–	**20**, 60, 200	–	**6.1**, 18, 60
Dog (beagle)	1 year [repeat-dose toxicity]	**0.3**, 1.0, 3.0	–	**6**, 20, 60	–	**1.8**, 6.1, 18
Human ADHD patients (♂ + ♀), 6–12 years of age, n = 14, mean weight = 34.7 kg	steady state [Clinical Study **SPD503-107**]	[4 mg]	162.1	3.3[e]	–	–

[a] = animal: human plasma; [b] = BSA conversion factors for mg/kg to mg/m^2: human child (35 kg) = 29, mouse = 3, rat = 6, dog = 20; [c] = no data available; [d] = doses adjusted to reflect weekly exposure; [e] = The 3.3 mg/m^2 clinical dose has been calculated for the patient group in Study SPD503-107. Based on the 'Dosage and Administration' section of the PI, the MRHD is 0.12 mg/kg/day over the body weight range 25 - ≥91 kg, up to a maximum of 7 mg/day. Thus, the BSA dose could range from 3.1 mg/m^2/day (25 kg patient, BSA conversion factor 26) to 4.2 mg/m^2/day (60 kg patient, BSA conversion factor 35); for patients > 60 kg, the 7 mg/day upper dose limit reduces the mg/kg (and mg/m^2) daily dosage. The most conservative calculation has been chosen for relevant PI statements.

Effects of guanfacine on organs and bodily systems are outlined below:

Alimentary tract: Oesophagus, stomach and small and large intestine showed evidence of inflammation (inflammatory cell infiltration, arteritis) in rats receiving 2 x 7.5 mg/kg/day for 5 days or 2 x 7.5/10 mg/kg/day for 10 days, at exposure ratios of 3.7 and 22, respectively. Female rats receiving guanfacine at 6.19 mg/kg/day via their diet for 102 weeks showed diffuse dilation and wall thickening of the small and large intestine.

Eye: Mice dosed at approximately 10 mg/kg/day via their diet for 78 weeks showed an increased incidence of corneal opacity. Rats dosed orally at 30 mg/kg/day for 5 weeks also showed corneal opacity. This effect was attributed to irritation caused by xerosis and mechanical stimulation following exophthalmos.

Haemopoietic system: Male mice dosed at approximately 10 mg/kg/day via their diet for 78 weeks showed lymphopaenia. Red blood cell (RBC) parameters were increased rats dosed orally at 10 or 30 mg/kg/day for 5 weeks. However, dogs dosed for 90 days or 1 year showed dose related reductions in RBC parameters. Dogs dosed for 1 year at 1 or 3 mg/kg/day also showed atrophy and anaemia in the spleen.

Heart: No findings in rats. Dogs dosed at 10 mg/kg/day for 90 days showed evidence of fibrosis and lymphocytic infiltration. Dogs dosed for 1 year showed significant prolongation of the QT interval at 1 or 3 mg/kg/day and a dose related increase in incidence and intensity of notched T wave in all drug treated groups.

Kidney: Rats dosed orally at 10 or 30 mg/kg/day for 5 weeks showed a significant elevation of blood urea nitrogen, and there was a low incidence of histopathological renal changes in high dose (HD) female rats. Dogs dosed for 1 year showed reduced sodium excretion at the mid dose (MD) and HD, and reduced potassium excretion at the HD.

Liver: Showed evidence for irritation in rats dosed for 5 weeks at 3 mg/kg/day or higher: focal necrosis and perivascular infiltration of possible inflammatory cells. HD dogs from both the 90 day and 1 year studies showed various changes including discolouration (brown pigment in Kuppfer cells and haemorrhagic foci) and hyaline bodies and lipid accumulation in hepatocytes.

Spermatogenesis: Vacuolar changes in spermatogenic cells and reductions in spermatogenesis were seen in HD dogs from the 90-day study.

Valvulopathogenicity: Rats, both adult and juvenile, were dosed at up to 10 mg/kg/day of guanfacine hydrochloride for up to 94 days, and heart valve tissue sections were then examined for evidence of drug-induced proliferative activity or degeneration. No significant evidence for induction of valvulopathy was found. Repeat dosing with positive control compounds (fenfluramine/phentermine) also failed to induce valvulopathy in the rat heart and it was concluded that rats are not an appropriate model system for such studies.

Genotoxicity

Guanfacine was not mutagenic at up to 5000 µg/plate, in both the presence and absence of metabolic activation, in standard bacterial reverse mutation assays. Guanfacine was also negative for the induction of structural chromosomal aberrations, in an in vitro human peripheral blood lymphocyte clastogenicity assay, at concentrations up to 40 µg/mL (more than 5000 times the clinical steady state concentration) in the absence of metabolic activation or at 240 µg/mL in the presence of metabolic activation. There was, however, a low level increase in the frequency of numerical chromosomal aberrations (that is, endoreduplicated or polyploid cells) apparently associated with guanfacine exposure, although this result was not considered meaningful for human treatment. A shortcoming of these studies is that, because the metabolites of guanfacine found in human plasma have not been comprehensively identified and quantified, it is unclear whether metabolic activation of guanfacine with rat liver extract would produce a comparable range of metabolites.

ICH guideline S2[8] recommends that an in vivo test of genotoxicity also be performed. The FDA report on Tenex indicates that this has been done, although details (other than that guanfacine gave a negative result) were not available to this assessor.

Carcinogenicity

The FDA report on Tenex outlines carcinogenicity studies performed using mice and rats that were dosed with guanfacine hydrochloride via their diet for periods of 78 and 102 weeks, respectively (see Table 3 for doses and exposure ratios in these studies). There were no differences in tumour incidences between control and test article-treated mice. The MD and HD rat groups showed a higher incidence of pancreatic islet adenomas. Overall, however, there were no significant differences in tumour incidence between groups and it was concluded that guanfacine is negative for carcinogenicity in rats.

Reproductive toxicity

Relevant studies were performed using mice, rats, and rabbits given oral (gavage) doses of guanfacine hydrochloride. Information on these studies was taken from the FDA report on Tenex and from a series of 1979/1980 publications from a Japanese research institute. None of these studies reported toxicokinetic (TK) data. Accordingly, exposure ratio calculations used animal and human mg/m^2 values (Table 4).

Relative exposure

Relative exposures for each species, dose and study are detailed in Table 4 below.

Species	Study type [details]	Dosing period	Dose mg/kg /day]	mg/ m^2	Exposure ratio #
Mouse (JCL:ICR)	Fertility [Esaki and Hirayama (1979)]	♂ = 10 weeks (6 days/week) + every day till copulation; ♀ = 2 weeks + GD0–GD6	0.5	1.5	0.4
			1	3	0.9
			2	6	1.8
	Embryofetal development [Esaki and Hirayama (1979a)]	GD6–GD15	**0.5**	**1.5**	**0.4**
			1	3	0.9
			2	6	1.8
	Embryofetal development [Esaki *et al.* (1980)]	GD6–GD15	**0.5**	**1.5**	**0.4**
			1	3	0.9
			2	6	1.8

[8] ICH Harmonised Tripartite Guideline. Guidance On Genotoxicity Testing And. Data Interpretation For Pharmaceuticals Intended For Human Use.

Species	Study type [details]	Dosing period	Dose mg/kg /day]	mg/ m²	Exposure ratio #
	Pre-/postnatal development [Esaki and Hirayama (1979b)]	GD15–PND20	**0.5**	**1.5**	**0.4**
			1	3	0.9
			2	6	1.8
Rat (RAC)	Fertility [FDA report on Tenex]	♂ = 80 days (mated with untreated females); ♀ = 12 days + GD0–GD5 (mated with untreated males)	8	48	14
			16	96	29
Rat (OFA)	Embryofetal development [FDA report on Tenex]	GD6–GD15	1	6	1.8
			3	**18**	**5.4**
			10	60	18
Rat (RAC)	Pre-/postnatal development [FDA report on Tenex]	GD15–PND21	2	12	3.6
			4	**24**	**7.2**
			8	48	14
Rabbit ('hare-type' (presumably Belgian hare variety))	Embryofetal development [FDA report on Tenex]	GD6–GD18	0.5	7.5	2.2
			1	**15**	**4.5**
			5	75	22
Rabbit (NZW)	Embryofetal development [Esaki and Nakayama (1979)]	GD6–GD18	**0.5**	**7.5**	**2.2**
			1	15	4.5
			2	30	9.0
Human ADHD patients (♂ + ♀), 6–12 years of age, n = 14, mean	steady state [Clinical Study SPD503-107]	–	[4 mg]	3.3^	–

Species	Study type [details]	Dosing period	Dose mg/kg /day]	mg/ m^2	Exposure ratio #
weight = 34.7 kg					

= animal: human plasma ^ BSA dose range is 2.9-4.2 mg/m^2/day (see footnote to Table 3)

Exposure ratios achieved at the NOAEL doses (bolded values in Table 4) in the reproductive toxicity studies were low for all species examined. Indeed (as noted above), mg/m^2 derived values likely exaggerate the true exposure ratio due at least in part to the much higher rate of guanfacine metabolism in rodents as compared to humans. True exposure ratios at NOAEL doses are likely around 1 or less.

Guanfacine and/or its metabolites were excreted into rat milk and were able to cross the rat placenta and enter fetal tissues (albeit at concentrations approximately 5 to 10-fold lower than those in the corresponding maternal tissue).

Guanfacine dosing showed no consistent effects on fertility of male and female mice and rats at all doses tested. Evaluation of the effects of guanfacine on embryonic and fetal development used mice, rats, and rabbits. Mice receiving 1 or 2 mg/kg/day (doses producing exposures that are likely comparable with those from proposed human doses), from gestational day (GD) 6 to GD 15, showed decreased fetal weight and increases in the incidences of fetal death and malformations. The sponsor has argued that the finding of teratogenicity in mice is not of general significance ('*…these findings are considered specific to mice which are susceptible to exencephaly and spinal changes following malnutrition during pregnancy*.'). Rats dosed at up to 10 mg/kg/day showed no evidence of fetal malformations, although such a dose produced a decrease in fetal weight gain and fetal deaths. Similarly, there was no evidence for teratogenicity in rabbit dams receiving up to 5 mg/kg/day, although such doses produced deaths and decreased body weight gain in dams and fetal toxicity.

The effects of pre-/postnatal dosing (GD15 to postnatal day (PND) 20/21) were tested using mice and rats given up to 2 and 8 mg/kg/day of guanfacine, respectively. There was no apparent effect of dosing on pup development, although HD litters showed decreased pup weight and increased deaths probably due to guanfacine-induced decreased lactation capacity of the dams. Pre/postnatal dosing of rats at up to 4 mg/kg/day had no adverse effects on the reproductive performance of the next (F_1) generation.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3[9]. This categorisation is appropriate given the results of animal studies.

Local tolerance

No studies in this area were performed. As Intuniv is for oral administration, this is reasonable and consistent with ICH M3.

[9] Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Immunotoxicity

No newer studies focussed on this area were presented. Older rat and dog repeat-dose toxicity studies, performed for the registration of Tenex, did not indicate effects of guanfacine on the spleen, thymus, or lymph nodes. However, a literature study indicated changes in white blood cell ratios in rats receiving relatively high doses of guanfacine for 5 weeks. It would appear unlikely that such findings have clinical relevance.

Phototoxicity

The sponsor's studies demonstrated that guanfacine does not absorb electromagnetic radiation in the wavelength range 250 to 400 nm. Wavelengths shorter than about 280 nm (which could be absorbed by guanfacine) are completely absorbed by the ozone layer and the atmosphere. In addition, guanfacine does not show preferential distribution into melanin-containing tissues. Accordingly, guanfacine is unlikely to produce phototoxicity.

Metabolites

Because of the prominence of phase II reaction products in the plasma of both man and animal species (see above), and the usual lack of toxicological risk associated with such products, toxicology studies were not performed with these metabolites. This is reasonable. The sponsor did, however, submit a new study examining the possible pharmacodynamic activity of 3-hydroxyguanfacine-*O*-sulfate at human α2A-, α2B- and α2C-Ad receptors. No evidence was found for either agonist or antagonist activity at any of these adrenoceptor subtypes.

Paediatric use

In support of the use of Intuniv for the treatment of ADHD in children and juveniles, the sponsor submitted nonclinical studies examining the effects of oral dosing of juvenile rats with guanfacine hydrochloride. However, the apparent differences in guanfacine metabolism between rats and humans (see above) raise questions as to whether the juvenile rat is an appropriate model for extrapolation to humans.

$AUC_{0-24/12\,h}$ values were determined in several studies in which juvenile rats of both sexes were given a daily dose of guanfacine hydrochloride from PND7 onwards. NOAEL doses (bolded values in Table 5) in these studies were ≤ 1.0 mg/kg/day. The exposure ratios, as calculated using AUC values, were less than unity at the NOAEL dose for both sexes in each of the studies; whilst C_{max} values, at the end of the dosing period in rats receiving the NOAEL dose (1.5 to 5 ng/mL), were less than half of those at steady state in ADHD patients receiving the maximum recommended dose (10 ng/mL). The mg/m^2 derived exposure ratios were consistently higher (up to approximately 10-fold greater) than those determined from AUC values. It was also notable that AUC values, in rat pups of both sexes, declined significantly with age (≥ 2 fold decrease between PND7 and PND59). This decline could be attributable to a maturity-related increase in the levels of guanfacine-metabolising enzymes in the rat liver. The clinical relevance of this finding is, however, doubtful as, beyond about 6 months of age, hepatic catalytic activity of various CYP enzymes (including CYP3A4/5) is comparable between children and adults.[10]

The major dose limiting response seen in juvenile rats was a dose-dependent decrease in weight gain. In contrast, children taking guanfacine for treatment of ADHD may be at

[10] Ginsberg G., Hattis D., Sonawane B., Russ A. et al. (2002) Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. Toxicological Sciences, 66: 185–200. Blanco J.G., Harrison P.L., Evans W.E. and Relling M.V. (2000) Human cytochrome P450 maximal activities in pediatric versus adult liver. Drug Metabolism and Disposition, 28: 379–382.

increased risk of excessive weight gain.[11] Studies in juvenile rats examined possible interaction between guanfacine and methylphenidate hydrochloride (Ritalin). Exposure values (both C_{max} and AUC) for guanfacine, for both sexes and on both PND13 and PND53, were increased by a factor of approximately 2 to 4 following co-administration with methylphenidate as compared to administration of guanfacine alone. However, co-administration of guanfacine and methylphenidate had no consistent effect on exposure to methylphenidate. The basis for the effect on guanfacine exposure was not explored. In humans, the majority of orally administered methylphenidate undergoes de-esterification to an inactive metabolite.[12] The increased exposure to guanfacine did not appear to produce changes of toxicological concern and the NOAEL dose was 1 mg/kg/day of guanfacine with or without 50 mg/kg/day of methylphenidate (both sexes).

Study details	Dosing period	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)		mg/m^2 [b]	Exposure ratio[a]		
						AUC_{0-24h}		mg/m^2
			♂	♀		♂	♀	
R00697-SPD503	PND7–PND48 [PND7–PND14]	0.5, 1.0, 3.0 [5.0, 10.0]	–[c]	–	3, 6, 18 [30, 60]	–	–	0.9, 1.8, 5.4 [9, 18]
R00242-SPD503-IIIC	PND7–PND59	0.3, **1.0**, 2.0 (♂) or 3.0 (♀)	PND14 = 7.72, 37.76, 84.63; PND53 = 2.01, 19.0, 22.06	7.63, 46.43, 165.75 1.31, 21.35, 56.07	1.8, 6, 12 or 18	0.05, 0.23, 0.52; 0.01, 0.12, 0.14	0.05, 0.29, 1.0 0.01, 0.13, 0.35	0.5, 1.8, 3.6 or 5.4
R3799M-SPD503	PND7–PND97	**0.3**, 1.0, 3.0	PND13 = 9.81, 63.1, 261 PND96 = 4.70, 21.3, 94.3	11.1, 54.2, 358 5.55, 29.1, 168	1.8, 6, 18	0.06, 0.39, 1.6 0.03, 0.13, 0.58	0.07, 0.33, 2.2 0.03, 0.18, 1.0	0.5, 1.8, 5.4
R01587M-SPD503	PND7–PND59	**1.0**	PND13 = 68.94[d] PND53 = 9.35[d]	73.53[d] 16.15[d]	6	0.43 0.06	0.45 0.10	1.8

[11] Khan M.A., Jain G., Soltys S.M. and Takahashi A. (2012) A case of excessive weight gain with guanfacine extended release: 9.53 kg in 4 weeks. Journal of Child and Adolescent Psychopharmacology, 22: 256–257. Siddiqi S.U., Giordano B.P. and Dedlow E.R. (2015) Excessive weight gain with guanfacine: 16.1 kilograms in 12 months. Clinical Pediatrics, 54: 793–795.

[12] Markowitz J.S., DeVane C.L., Boulton D.W., Nahas Z. et al. (2000) Ethylphenidate formation in human subjects after the administration of a single dose of methylphenidate and ethanol. Drug Metabolism and Disposition, 28: 620–624.

Study details	Dosing period	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)		mg/m^2 [b]	Exposure ratio[a]		
						AUC_{0-24h}		mg/m^2
			♂	♀		♂	♀	
Human ADHD patients	steady state [Clinical Study **SPD503-107**]	[4 mg]	162.1		3.3^	–		–

[a] = rat: human plasma; [b] = conversion factors for mg/kg to mg/m^2: human child (35 kg) = 29, rat = 6 (however, may be over-estimate for younger animals); [c] = no data available; [d] = AUC_{0-12h}^ BSA dose range is 2.9-4.2 mg/m^2/day (see footnote to Table 3)

Nonclinical summary

- Guanfacine has been marketed for the treatment of hypertension in an immediate-release form in Europe as Estulic since 1979 and in USA as Tenex since 1986. Intuniv (an extended release form of guanfacine) has been approved in the USA for the treatment of ADHD since 2009. Accordingly, the material examined in producing this assessment included the FDA reviews of Tenex and Intuniv, literature reports of clinical and nonclinical studies performed using guanfacine, and some newer studies (performed in response to deficiencies noted by other drug regulators) provided by the sponsor. Much of the primary data on guanfacine has not been sighted by the assessor and some of the opinions expressed in this report are based on the assessments of others. Because many of the studies referenced in this assessment date from the 1970s, 1980s and 1990s, they are not as comprehensive as more modern studies and not GLP compliant. Accordingly, this assessment is based on data of rather uneven quality. There is, however, reassurance in that the properties of guanfacine have been assessed by many laboratories and the medicine has been in clinical use for many years (albeit in a different population age group to that now intended).
- Guanfacine shows moderately strong binding affinity (Ki = 13.3 nM) for human recombinant α2A-Ad receptor. By comparison, ADHD patients given the proposed maximum dose had a plasma C_{max} of 41 nM, a mean plasma concentration at steady state of 27 nM, and an unbound C_{max} of approximately 12 nM. Studies in animal models (rats, monkeys) have shown that guanfacine can improve ADHD related behaviours, and such improvement has been correlated with increased neuronal activity in the PFC.
- Guanfacine showed low affinity, at clinically relevant concentrations, towards a panel of various proteins (primarily neurotransmitter receptors). In functional assays, guanfacine showed specificity for agonist activity at α2A-Ad receptors, being approximately 7 and approximately 10 fold less active at α2B- and α2C-Ad receptors, respectively. In contrast, clonidine (another adrenergic receptor agonist that has been used to treat ADHD) showed comparable activity at α2A- and α2B-Ad receptors. Guanfacine was approximately 1000 times less effective than serotonin at activating 5-HT2B receptors in a functional assay (EC_{50} = 4.1 x 10^{-8} and 4.5 x 10^{-11} M, respectively).

- Safety pharmacology studies assessed effects on the cardiovascular, excretory, and respiratory systems. Guanfacine was shown to inhibit defecation in mice and to have a diuretic effect in rats and dogs. Such effects may be related to the GI-tract-associated adverse events that are commonly noted in patients taking guanfacine. No significant inhibition of hERG K+ channel tail current was observed at guanfacine concentrations up to approximately 4 μM (> 300 times clinical C_{max}, unbound). Guanfacine dosing of dogs produced a pronounced and prolonged bradycardia. Hence, clinical use might be expected to produce bradycardia but not QT interval prolongation. Contradictory effects of guanfacine on respiration have been noted in animal studies and it is difficult to assess their relevance to human treatment.
- Immediate-release guanfacine hydrochloride showed rapid absorption following oral dosing of rats, dogs, and monkeys, with T_{max} at 0.5 to 2 h post dosing and also showed rapid absorption by humans (T_{max} approximately 2 to 3 h). However, T_{max} in adult humans for Intuniv tablets, which are an extended-release formulation of guanfacine hydrochloride, was approximately 6 h. The bioavailability of guanfacine hydrochloride appears to be high in humans (> 80%) and in various animal species. Studies using juvenile rats suggested that C_{max} and AUC values generally increased in a more than dose proportional manner over the range 0.3 to 3 mg/kg/day PO. However, the sponsor's studies suggested that C_{max} and AUC values increased approximately dose proportionally in children and adolescents with ADHD. Plasma terminal $t_{½}$ values for rats orally administered guanfacine were approximately 2 to 5 h, whereas values for children and adult humans were in the range 13 to 23 h. Limited protein binding data, for human plasma only, indicated moderate (approximately 70%) binding of guanfacine. The tissue distribution of guanfacine following oral dosing of rats was wide, although penetration into the brain (the target organ) was low. A comprehensive identification and quantification of the human metabolites of guanfacine does not appear to have been performed, although it is claimed that 3-hydroxy guanfacine and its glucuronide and sulfate conjugates are the major metabolites found in human plasma. The major circulating metabolites in animal species were dihydro-diol guanfacine (dog) and sulfate conjugates of hydroxy guanfacine (rat, dog, and cynomolgus monkey). Hence, there is some overlap between the human and animal metabolites. In vitro studies suggested that guanfacine is predominantly metabolised by CYP3A4 and this was supported by the finding that exposure in humans was increased by co-administration of ketoconazole. After oral dosing, guanfacine related material was excreted in both urine and faeces by rats, whereas urine was the predominant route of excretion for dogs, cynomolgus monkeys, and humans.
- Rats and, to a lesser extent, mice were the species primarily used to explore toxicity issues associated with guanfacine hydrochloride. Pharmacokinetic, metabolic, and other results (for example valvulopathogenicity (see above)) suggest, however, that rodents are likely a poor base for extrapolation to humans.
- Aside from having low affinity for OCT1 (Km = 11.2 μM) and OCT2 (Km = 4.5 μM), guanfacine did not interact significantly with various transporters and at concentrations up to 10 μM did not significantly inhibit various UGT enzymes. Studies with human hepatic microsomes and with human hepatocytes provided no indication that the concentrations of guanfacine occurring in patients are likely to inhibit or induce CYP enzyme activities. As noted above, strong CYP3A4 inhibitors may increase guanfacine exposure. These results suggested that guanfacine has a low potential for interaction with co-administered drugs.
- Guanfacine hydrochloride showed high toxicity in mice but more moderate toxicity in rats. Deaths occurring soon after test article administration were attributed to respiratory paralysis.

- Repeat-dose toxicity studies were conducted in adult mice (78 week carcinogenicity study; dietary intake), rats (up to 102 week carcinogenicity study; dietary intake), and dogs (up to 1 year; dosing by capsule). Maximum exposures (mg/m^2) were modest in all species and true exposure ratios were likely near or less than unity at NOAEL doses. However, due to the lack of toxicokinetic data, accurate exposure ratio values were not available. A consistent finding from the studies with rats and dogs was an association between guanfacine dosing and failure to gain or loss of weight. This finding could be due to the induction of hyperglycaemia by guanfacine. There was, however, no indication from long-term patient studies for guanfacine induced increases of blood glucose. Other findings included: diffuse dilation and wall thickening of the small and large intestine in female rats dosed at approximately 6 mg/kg/day via their diet for 102 weeks; fibrosis and lymphocytic infiltration in the heart of dogs dosed at 10 mg/kg/day for 90 days; lymphopaenia in male mice dosed at approximately 10 mg/kg/day via their diet for 78 weeks and changes in RBC parameters in rats and dogs; and vacuolar changes in spermatogenic cells and reductions in spermatogenesis in dogs dosed at 10 mg/kg/day for 90 days. The changes seen in rodents are likely of questionable relevance to humans nevertheless the effect on male fertility in dogs could be significant for clinical use.
- Repeat-dose toxicity studies were also performed with juvenile rats (as a model for the treatment of ADHD in children/juveniles). Toxicokinetic data were provided with these studies and showed that exposure ratios (derived from AUC values) were less than unity at the NOAEL dose for both sexes. The major dose limiting response seen in juvenile rats was decreased weight gain. In contrast, children taking guanfacine for treatment of ADHD may be at increased risk of excessive weight gain.
- It has been suggested that long-term use of guanfacine could be associated with a significantly increased risk of cardiac disease due to the activation of the 5-HT2B receptor leading to mitogenic activity of fibroblasts in the heart valves. No evidence for heart valve changes was found in adult or juvenile rats dosed with guanfacine hydrochloride at up to 10 mg/kg/day for 94 days. However, drugs known to be valvulopathogens in humans had no significant effects on the rat heart and it was concluded that rats are not an appropriate model for this disease. As noted above, guanfacine was shown to be a relatively weak activator of 5-HT2B receptors. In addition, the FDA review of Intuniv notes that: '*there have not been any reports of valvulopathy for guanfacine in humans submitted to FDA … despite a long history of use'*. And, in most assays of 5-HT2B receptor activation, guanfacine showed significantly lower potency than known human valvulopathogens.[13] Accordingly, it appears unlikely that guanfacine is a valvulopathogen in humans.
- Guanfacine was not mutagenic in standard bacterial reverse mutation assays or clastogenic in an in vitro human lymphocyte assay. Carcinogenicity studies were performed using mice and rats that were dosed with guanfacine hydrochloride via their diet for periods of 78 and 102 weeks, respectively. Toxicokinetic data were not obtained in these studies and true exposure ratios at the high dose were likely near unity. No treatment-related increase in overall tumour incidence was observed in either mice or rats.
- Reproductive toxicity studies were performed using mice, rats and rabbits. Exposure ratios, particularly for mice, were low and at NOAEL doses were likely unity or less. There were no consistent effects of guanfacine dosing on fertility in male and female mice and rats. Both rats and rabbits showed no evidence for induction of fetal

[13] Huang X.P., Setola V., Yadav P.N., Allen J.A. et al. (2009) Parallel functional activity profiling reveals valvulopathogens are potent 5-hydroxytryptamine2B receptor agonists: implications for drug safety assessment. Molecular Pharmacology, 76: 710–722.

malformations, although higher doses of guanfacine induced fetal toxicity in both species. Mice showed induction of fetal malformations at guanfacine doses producing fetal toxicity and decreased fetal weight. This effect is not considered to be of more general significance as mice are known to be susceptible to induction of malformation if malnutrition occurs during pregnancy.[14] There were no apparent effects of pre-/postnatal dosing on mouse and rat pup development, although at high doses there was decreased pup weight and increased deaths probably due to guanfacine induced decreased lactation by dams.

Nonclinical conclusions

- There are significant deficiencies in the nonclinical data. However, this assessor does not consider them so serious as to preclude registration.
- The primary pharmacology studies support the treatment of childhood/juvenile ADHD with guanfacine.
- Secondary pharmacodynamics studies did not indicate likely off-target effects. Safety pharmacology studies showed that guanfacine can inhibit defecation in mice, have a diuretic effect in rats and dogs and can produce bradycardia in dogs.
- Pharmacokinetic drug interaction studies did not indicate issues of concern for clinical use.
- Repeat-dose toxicity studies were largely based on the use of rodents. However, various results suggested that rodents are poor models for human use of guanfacine. An effect of guanfacine dosing on male fertility in dogs could be significant for clinical use.
- Guanfacine is not considered to pose a genotoxic or carcinogenic hazard.
- The proposed pregnancy Category (B3) is reasonable.
- There are no nonclinical objections to registration.
- The nonclinical evaluator proposed amendments to the draft Product Information (PI) document but these are beyond the scope of this AusPAR.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Information on the condition being treated

The following background information comes from The Mental Health of Children and Adolescents Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing.[15]

[14] Runner M.N. and Miller J.R. (1956) Congenital deformity in the mouse as a consequence of fasting. Anatomical Record, 124: 437–438.
[15] Lawrence D, Johnson S, Hafekost J, Boterhoven de Haan K, Sawyer M, Ainley J, Zubrick SR. Mental Health of Children and Adolescents Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Commonwealth of Australia (2015) ISBN: 978-1-76007-187-5

ADHD is a persistent pattern of inattention and/ or hyperactivity-impulsivity more frequent and severe than in other individuals at a similar developmental stage. There are three subtypes of ADHD based on the most common symptoms. Those with mostly inattentive symptoms are diagnosed with ADHD, predominantly inattentive type and individuals with primarily hyperactivity-impulsivity symptoms are diagnosed with ADHD, predominantly hyperactive-impulsive type. Those children and adolescence with symptoms of both inattentiveness and hyperactivity are diagnosed with ADHD, combined type. The DSM-IV criteria[16] require at least six symptoms of either inattention or hyperactivity-impulsivity to have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. Symptoms must be present in at least two settings (for example, at school and at home), and some symptoms causing impairment must have been present before the age of 7 years.

The prevalence of ADHD in Australian children and adolescents is 7.4%, equivalent to an estimated 298,000 children and adolescents. Of the three sub-types of ADHD, inattentive type was the most common, with 3.4% of children and adolescents having inattentive type, 1.2% hyperactive type and 2.8% combined type. The prevalence of ADHD was higher in males than females, with more than twice as many males as females having had ADHD in the previous 12 months (10.4% compared with 4.3%).

The severity of impact of ADHD on children and adolescents in four different domains (school or work, friends and social actives, family and impact on self) and overall is reported in Table 1 in Attachment 2. Overall one in ten (10.5%) children and adolescents with ADHD had severe impact on functioning in at least one of these domains. Severe impact on functioning was reported most commonly in the domain of family (17.3%), and then school or work (12.8%). Only 3.7% of children and adolescents with ADHD had a severe level of impact on functioning in the self-domain (that is, where the young person experienced a high level of distress due to their symptoms). Two fifths (40.9%) of children and adolescents with ADHD had no impact in the friends domain, while only 13.3% of children with ADHD had no impact in the school or work domain.

Current treatment options

Pharmacological approaches are usually used in managing ADHD in Australia. Current pharmacological treatment options available in Australia include:

- Central nervous system (CNS) stimulants
  - Methylphenidate
  - Dexamfetamine
  - Lisdexamfetamine
- Atomoxetine (selective inhibitor of norepinephrine reuptake)

Non-pharmacological interventions include general behavioural approaches and cognitive behavioural therapy.

Clinical rationale

The sponsor has identified the following situations where an alternative to psychostimulants would be desirable:

- A subset of ADHD patients will fail to respond to stimulant monotherapy.

[16] DSM-IV Codes are the classification found in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, also known as DSM-IV-TR, a manual published by the American Psychiatric Association (APA) that includes all currently recognized mental health disorders.

- A subset of ADHD patients will have side effects that preclude stimulant use, for example insomnia and anorexia with stimulants.
- In some children treated with psychostimulants, ADHD symptoms may not be adequately controlled in the hours before school or in the evening. In addition, some stimulants have a short duration of action, requiring multiple doses per day, which can result in compliance problems, especially in children.
- Psychostimulants may also have limitations in the treatment of some patients with comorbid symptoms (for example, oppositional defiant disorder, anxiety disorder, substance abuse, tics, and Tourette's syndrome).
- Patients in whom stimulants or other non-stimulants (that is, atomoxetine) are contraindicated.
- In addition, physicians and/or parents may prefer a treatment option which is not a controlled substance due to the potential for abuse or dependence.

The sponsor gives the following rational for developing guanfacine:

'*Several studies published in peer reviewed journals have documented the beneficial effects of guanfacine and other alpha-2-adrenergic agonists (such as clonidine) for treatment of the symptoms of ADHD. Shire has developed a modified-release version of guanfacine HCl (SPD503) as an additional alternative non-stimulant option for the treatment of ADHD*.' The studies referred to were not cited by the sponsor.

The rationale for developing guanfacine is not clear. The sponsor mentions published data in the statement: '*Several studies published in peer reviewed journals have documented the beneficial effects of guanfacine and other alpha-2-adrenergic agonists (such as clonidine) for treatment of the symptoms of ADHD*.' However, the sponsor does not provide references for these data.

The indication sought by the sponsor is similar to that which is approved in the USA but the EU indication is much more restrictive. The EU indication requires prior treatment with CNS stimulants to be '*not suitable, not tolerated or have been shown to be ineffective.*'

Guidance

The following guidance applies to the present application:

- EMA/CHMP/185423/2010 Rev 2. Guideline on clinical investigation of medicinal products in the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
- CHMP/ICH/2/04. ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Contents of the clinical dossier

The dossier represented a development program for guanfacine extended release (SPD503) in children and adolescents with ADHD.

- There were 15 studies with pharmacokinetic data.
- There were two studies with pharmacodynamic data
- There was one population pharmacokinetic-pharmacodynamic study
- There were eight pivotal studies conducted in children and adolescents with ADHD
- There were three long-term follow-on studies.
- There were three other efficacy and safety studies.

- There were two other safety studies.

Paediatric data

Data relating to children and adolescents aged 6 to 17 years is included in the dossier.

Good clinical practice (GCP)

The clinical studies presented in the dossier are stated to have adhered to GCP and appear to have adhered to GCP.

Evaluator's commentary on the clinical dossier

The clinical dossier represents a complete clinical development program in a specific population (that is, children and adolescents with ADHD).

Pharmacokinetics

Studies providing pharmacokinetic data

The following table summarises the pharmacokinetic studies submitted by the sponsor.

Table 6: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
General Pharmacokinetics	General PK - Multi-dose	Study SPD503-113	*
		Study 1209A3111	*
		Study SPD503-206	*
	Bioequivalence † - Single dose	Study SPD503-101	*
		Study SPD503-103	*
		Study SPD503-110,	*
		Study SPD503-119	*
		Study SPD503-120	*
	Food effect	Study SPD503-104	*

PK topic	Subtopic	Study ID	*
PK in special populations	Target population § - Multi dose	Study SPD503-107	*
PK interactions	Ketoconazole	Study SPD503-106	*
	Rifampicin	Study SPD503-108	*
	Methylphenidate	Study SPD503-114	*
	Lisdexamphetamine (*d*-amphetamine)	Study SPD503-115	*
Population PK analyses	Target population §	Study SPD503-312	*

* Indicates the primary PK aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of guanfacine has been adequately characterised. Guanfacine in the extended release formulation (SPD503) has a favourable PK profile for use in children and adolescents with ADHD.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no new data in the dossier examining primary pharmacology. The following table summarises the pharmacodynamic studies submitted with this application.

Table 7: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Secondary Pharmacology	Effect on PD parameter: blood pressure	Study SPD503-102	
	Effect on PD parameter: QTc prolongation	Study SPD503-112	
Population PD and PK-PD analyses	Target population	Study SPD503-312,	

* Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

Evaluator's conclusions on pharmacodynamics

In the dose range studied, the plasma concentration effect relationship was linear. There were no rebound effects on blood pressure with the extended release formulation.

Dosage selection for the pivotal studies

The sponsor has investigated tolerability, safety and efficacy in the dose range 1 mg to 7 mg per day. The final dosing used in the clinical trials was a weight based dosing regimen that reflected the findings of the dose finding studies. This weight based dosing regimen supports the dosing recommendations in the draft PI document.

Efficacy

Studies providing efficacy data

There were eight pivotal efficacy studies conducted in children and adolescents with ADHD. Studies were performed as monotherapy and as co-medication with psychostimulants. A study was also conducted in children and adolescents with ADHD and oppositional features. There were five supportive efficacy studies including two long-term follow-on studies.

Evaluator's conclusions on efficacy

The pivotal studies have demonstrated efficacy in comparison with placebo for guanfacine in comparison with placebo in subjects with ADHD aged 6 to 17 years. Study SPD503-312, Study SPD503-315 and Study SPD503-316 all had a maintenance phase ≥ 6 weeks in duration. The studies used outcome measures for both symptomatic and functional domains. The primary efficacy outcome measure was ADHD-RS-IV[17] which was used for inclusion and for efficacy. SPD503-315 used a responder category that was based on ADHD-RS-IV and Global Impressions-Severity or -Improvement (GCI-S). A pooled analysis of Study SPD503-316 and Study SPD503-312, there was significant improvement in all the domains of the functional score WFIRS-P (Weiss Functional Impairment Rating Scale-Parent Form) with the exception of Child Self-concept and Risk.

Efficacy was demonstrated for oppositional symptoms in subjects with ADHD with oppositional symptoms in Study SPD503-307.

A linear dose response up to 0.17 mg/kg/day was demonstrated in Study SPD503-301 and Study SPD503-304.

There is support for maintenance of efficacy for up to 24 months. Study SPD503-315 for 26 weeks. Study SPD503-303 and Study SPD503-305 were supportive of efficacy for up to 2 years.

There was no significant difference in efficacy between morning and evening dosing of guanfacine in Study SPD503-313 and Study SPD503-314.

[17] The ADHD Rating Scale-IV obtains parent ratings regarding the frequency of each ADHD symptom based on DSM-IV criteria. Parents are asked to determine symptomatic frequency that describes the child's home behaviour over the previous 6 months. The ADHD Rating Scale-IV is completed independently by the parent and scored by a clinician. The scale consists of 2 subscales: inattention (9 items) and hyperactivity-impulsivity (9 items). If 3 or more items are skipped, the clinician should use extreme caution in interpreting the scale. Results from this rating scale alone should not be used to make a diagnosis. Cited from Psych Congress Network https://www.psychcongress.com/saundras-corner/scales-screeners/adhd/adhd-rating-scale-iv-adhd-rs

Efficacy is supported in subjects with ADHD who are also taking psychostimulants. The dose of guanfacine tested in the study (Study SPD503-313) was up to 4 mg daily. This is less than the maximum dose in comparable age groups (that is, up to 7 mg/day in the 13 to 17 years age group).

Efficacy was not demonstrated separately for the inattentive subtype of ADHD. A subgroup analysis was performed in Study SPD503-301 but not in subsequent studies. This subgroup analysis did not show efficacy in the subgroup of subjects with inattentive type ADHD.

Improvement in quality of life scores (Health Utilities Index-2/3 (HUI-2/3)) was not demonstrated in any of the clinical studies.

There were no comparator controlled studies. In Study SPD503-316 a group treated with atomoxetine was included to provide 'reference data' but no formal comparison of efficacy was either planned or conducted. However in that study the effect sizes of guanfacine and atomoxetine were comparable.

There is no evidence of efficacy in subjects with comorbid conditions including: any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic stress disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis, or conduct disorder. Subjects with these comorbid conditions were excluded from the pivotal studies.

The outcome measures used in the pivotal studies were a combination of symptomatic and functional scores. Symptomatic scores such as ADHD-RS-IV, Conners' Parent Rating Scale-Revised (CPRS-R), Conners' Teacher Rating Scale-Revised (CTRS-R), CGI-I and Parent's Global Assessment (PGA) measured changes in ADHD symptomatology and indicated benefit for guanfacine. New York Parent Rating Scale-School-Aged (NYPRS-S) and CPRS-R:L measured oppositional symptomatology and also indicted benefit. The results for the functional score WFIRS-P indicate benefit that became more apparent on the pooled analysis of Study SPD503-316 and Study SPD503-312. Quality of life outcome measures, such as long parent-report questionnaire (CHQ-PF50), child-report questionnaire (CHQ-CF87) and HUI-2/3 did not demonstrate benefit for guanfacine. All of these outcome measures have been appropriately validated and are acceptable outcome measures for children and adolescents with ADHD.

The pivotal studies were well designed. The outcome measures were appropriate. The inclusion criteria, whilst restrictive, still represent the general population of children and adolescents with ADHD in Australia. The studies were adequately powered. The statistical techniques were appropriate. There were adequate measures taken to account for multiplicity. There were few dropouts during the study and few subjects excluded from analysis.

The dosing regimen proposed by the sponsor in the draft PI document is supported by the pivotal studies. This is a weight based dosing regimen, which was used in the pivotal studies.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

Pivotal and/or main efficacy studies

The pivotal efficacy studies examined the following safety variables:

- Adverse Effects (AEs) including Treatment Emergent Adverse Effects (TEAEs), treatment related TEAEs, Serious Adverse Effects (SAEs), and discontinuations due to AEs (DAEs)
- Laboratory tests including clinical chemistry and full blood counts
- ECGs with particular attention to QTc prolongation
- Vital signs
- Sedative related events
- Treatment emergent psychiatric conditions, including suicidality

Other studies with evaluable safety data are described in Attachment 2.

Patient exposure

Overall exposure to guanfacine extended release (SPD503) was 2411 subjects, with 1718 aged 6 to 12 years and 693 aged 13 to 17 years at time of randomisation. There were 482 subjects exposed for ≥ 180 days, 235 subjects exposed for ≥ 360 days and 101 subjects exposed for > 720 days. Subjects were exposed to up to 7 mg/day and up to 0.16 mg/kg/day.

Safety issues with the potential for major regulatory impact

See Attachment 2 for details.

Postmarketing data

Guanfacine extended release (SPD503) was first launched in the US in September 2009. There were nine Post-Marketing Safety Update Reports provided in the dossier covering the time period up to 1 September 2015. A total of 3,243 subjects had been treated with SPD503 in clinical trials. The estimated cumulative worldwide patient exposure is 965,432 patient years of treatment.

During the period covered by the reports, there have been no actions taken for safety reasons such as withdrawals, suspensions, limits on indication, or lack of approval for safety reasons taken by regulators.

The Important Identified Risks are:

- Syncope
- Bradycardia
- Hypotension
- Sedative events
- Withdrawal blood pressure increased
- Weight increase

The Important Potential Risks are:

- Cardiac valvulopathy due to binding to 5HT-2B receptors
- QT prolongation
- Off-label use

- Blood glucose disorder

The Missing Information is:

- Use of GXR in pregnant or breastfeeding women
- Use of GXR in patients with renal or hepatic impairment
- Long-term safety (neurocognition in particular but also effects on growth, sexual maturation)
- Drug interactions

Evaluator's conclusions on safety

Overall the rate of TEAEs was higher in the guanfacine extended release group than in the placebo 2046 (84.9%) subjects compared with 620 (63.7%). In the guanfacine group, there were 1467 (85.4%) subjects aged 6 to 12 years with TEAEs and 579 (83.5%) aged 13 to 17 years. Compared to placebo, there was a higher rate of somnolence, headache, fatigue and sedation regardless of dose or age group treated with guanfacine.

Overall the rate of treatment related TEAEs was higher in the guanfacine extended release group than in the placebo 1765 (73.2%) subjects compared with 357 (36.7%). In the guanfacine group, there were 1275 (74.2%) subjects aged 6 to 12 years with TEAEs and 490 (70.7%) aged 13 to 17 years. Somnolence, sedation and headache were the most common treatment related TEAEs.

There were no deaths in the study program.

Overall the rate of SAEs was higher in the guanfacine extended release group than in the placebo 49 (2.0%) subjects compared with eight (0.8%). In the guanfacine group, there were 33 (1.9%) subjects aged 6 to 12 years with TEAEs and 16 (2.3%) aged 13 to 17 years. Syncope and sedation were the commonest SAEs in the guanfacine group.

Overall the rate of DAE was higher in the guanfacine extended release group than in the placebo 261 (10.8%) subjects compared with 13 (1.3%). In the guanfacine group, there were 200 (11.6%) subjects aged 6 to 12 years with DAE and 61 (8.8%) aged 13 to 17 years. Somnolence and syncope were the commonest reasons for discontinuation in the guanfacine group.

At doses titrated up to 8 mg, there was prolongation of QTcF[18] to the threshold of regulatory concern but there was no prolongation when QTc was calculated by subject-specific QTc (QTcNi) (Study SPD503-112). The mean (90% CI) for difference guanfacine-placebo, change for baseline in QTcF was 3.54 (0.78 to 6.29) at 6 hours post dose, and 7.61 (4.87 to 10.34) at 12 hours post dose. However, heart rate decreased by a mean of 20 beats per minute (bpm) in the guanfacine group. Subsequently, ECG data were collected for all of the Phase III and Phase II studies and no significant concerns with regard to QTc prolongation were identified in these data. Of note, subjects with known QTc prolongation or who were taking drugs known to prolong QTc were excluded from all of these studies.

Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) decreased from the first dose of guanfacine, and normalised over several months of treatment. With tapered withdrawal of guanfacine rebound hypertension was not clinically significant. Postural hypotension and syncope was reported in patients treated with guanfacine. The pivotal trials excluded subjects with hypertension or orthostatic hypotension.

[18] QT interval corrected (QTc) for heart rate using Fridericia's formula (QTcF).

Somnolence and sedation were common adverse events. The rate of somnolence/sedation increased with dose in the fixed dose studies but a dose effect was not apparent in the dose optimisation studies.

Adverse psychiatric changes were not identified as a safety issue. There was no apparent increase in suicidality with guanfacine.

The pivotal clinical trials excluded patients with a broad range of comorbidities and the dossier does not contain safety data for use in these patients. Typical exclusion criteria used in the development program were those from Study SPD503-313:

- Any current, controlled (requiring a prohibited medication or behavioural modification program) or uncontrolled, co-morbid psychiatric diagnosis (except ODD), including any severe co-morbid Axis II disorders or severe Axis I disorders such as Post Traumatic Stress Disorder (PTSD), bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder (OCD), substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis or conduct disorder that, in the opinion of the Investigator, contraindicate SPD503 treatment or confound efficacy or safety assessments.
- Subjects who are at suicide risk, any subject who has previously made a suicide attempt or those who are currently demonstrating active suicide ideation.
- Subject has a history of seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years).
- History or presence of known structural cardiac abnormalities, symptomatic cardiovascular disease, advanced arteriosclerosis, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, syncope, cardiac conduction problems (for example,, clinically significant heart block or clinically significant abnormality in QT or QTc interval and so on), exercise-related cardiac events including syncope and pre-syncope, clinically significant bradycardia or any other serious cardiac problem that may place a subject at increased vulnerability to the effects of a stimulant and/or α2-agonist medication.
- Subject has a family history of sudden cardiac death or ventricular arrhythmia.
- Subject has symptomatic or clinically meaningful orthostatic hypotension based on clinical judgment.
- History of controlled or uncontrolled hypertension.
- Current use of any prohibited medication or other medications, including herbal supplements that have CNS effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (bronchodilators are permitted).
- Current use of any medication including herbal supplements that affect BP or HR or are known to prolong the QT/QTc interval (excluding the subject's current ADHD medication).
- Morbidly overweight or obese, as defined by a body mass index (BMI) > 95th percentile.
- Weight less than 55 lbs (25kg).
- Weight greater than 176 lbs (80kg).
- Pregnancy or currently lactating.
- History of alcohol or other substance abuse or dependence, as defined by DSM-IV (with the exceptions of caffeine or nicotine) within the last year.

These exclusion criteria and the conditions they represent should be mentioned in the contraindications and warnings sections of the PI document.

First Round Benefit-Risk Assessment

First round assessment of benefit-risk balance

The clinical evaluator is not in a position to determine the benefit-risk balance. There are a number of issues that require clarification before this can be determined. These issues are:

- Efficacy for guanfacine extended release has not been demonstrated for inattentive subtype ADHD.
- The effects on driving and operating machinery of guanfacine extended release have not been determined.

First round recommendation regarding authorisation

The clinical evaluator is deferring recommendation for authorisation until the following issues have been resolved:

- Efficacy for guanfacine extended release has not been demonstrated for inattentive subtype ADHD.
- The effects on driving and operating machinery of guanfacine extended release have not been determined.

Second Round Evaluation of clinical data submitted in response to questions

For details of Clinical questions, the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

Table 10: Second round assessment of benefits

Indication	
Benefits	Strengths and Uncertainties
Guanfacine significantly improves ADHD symptomatology in patients aged 6 to 17 years with ADHD There is maintenance of efficacy for up to 24 months. Efficacy was demonstrated for oppositional symptoms in subjects with ADHD with oppositional symptoms. Guanfacine significantly improves ADHD symptomatology in patients aged 6 to 17 years with ADHD who are co-	Demonstrated by the pivotal studies: Study SPD503-312, Study SPD503-315 and Study SPD503-316. Study SPD503-315 demonstrated efficacy for 26 weeks. Study SPD503-303 and Study SPD503-305 were supportive of efficacy for up to 2 years. Demonstrated in Study SPD503-307. Demonstrated in Study SPD503-313 Study SPD503-316 was not designed as a comparator controlled study.

Indication	
medicated with psychostimulants Guanfacine has not been demonstrated to be superior or non-inferior to any currently approved treatment for ADHD. Efficacy has been demonstrated in patients with the inattentive subtype of ADHD.	Demonstrated by a post hoc analysis of Study SPD503-301, SPD503-304, Study SPD503-312 and Study SPD503-316.

Second round assessment of risks

Table 11: Second round assessment of risks

Risks	Strengths and Uncertainties
Guanfacine extended release (SPD503) has a favourable safety profile. Somnolence, sedation, fatigue and headache are very common adverse events. There were no deaths in the clinical trials. There were few SAEs. The commonest SAEs were somnolence, sedation and syncope Somnolence and syncope were the commonest reasons for discontinuation due to AE. Guanfacine causes a decrease in HR, SBP and DBP that returns to baseline following several months of treatment. Rebound hypertension can be avoided by tapered withdrawal. QTcF prolongation of regulatory concern was identified in the thorough QT study. Clinically significant prolongation of QTcF or QTcB was not identified in the subsequent clinical trials. Effects on operating machinery and driving have not been evaluated. There are no safety data for the 5 mg to 7 mg dose range in patients co-medicated with psychostimulants.	There is extensive exposure data to support this including a total of 3,243 subjects treated with SPD503 in clinical trials and an estimated cumulative worldwide patient exposure of 965,432 patient years of treatment. This is supported by the safety data presented in the dossier.

Second round assessment of benefit-risk balance

The benefit-risk balance of Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, 3 mg and 4 mg modified release tablets would be favourable if steps are taken to ameliorate the following risks:

- Use in doses above 4 mg in patients also treated with psychostimulants.
- Use in patients operating heavy equipment or driving
- Use in patients with a history of long QT syndromes
- Use in patients co-medication with drugs known to prolong the QTc interval

Second round recommendation regarding authorisation

The application for Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, 3 mg and 4 mg modified release tablets should be rejected for the following indication:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive).*

The reason for rejection is that Intuniv (guanfacine hydrochloride) has not been compared with currently approved treatments for ADHD, and therefore its place in the order of management of the condition is unknown.

Consideration could be given for approval of the following alternative indication:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) where psychostimulants, atomoxetine and/or behavioural treatments have been ineffective or are contraindicated.*

VI. Pharmacovigilance findings

Summary

- Shire Pty Ltd submitted the AUS-RMP version 1.0 dated 15 April 2016 (data lock point (DLP) 31 December 2015) in the initial application dossier. During the submission assessment, the RMP evaluator requested the sponsor to submit an EU-RMP with Australian Specific Annex (ASA) according to the TGA's RMP guidance. The EU-RMP version 1.5 dated 15 April 2016 (DLP 31 December 2015) was provided in response to this request without an ASA. As no ASA has been submitted, the AUS-RMP version 1.0 and EU-RMP version 1.5 were considered in the first round RMP evaluation report. The sponsor submitted the ASA version 1.0 dated 16 February 2017 to the EU-RMP 1.5 with their response to the round 1 RMP evaluation report.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below. In their response to the first round RMP evaluation report, the sponsor has provided justification to not listing QT prolongation as a safety concern in the ASA.

R=routine and A=additional

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Bradycardia	✓	✓[3]	✓	✓
	Syncope	✓	✓[3]	✓	✓
	Hypotension/decreased blood pressure	✓	✓[3]	✓	✓
	Withdrawal blood pressure increase	✓	-	✓	✓
	Sedative events	✓	✓[3]	✓	✓
	Weight increase	✓	✓[3]	✓	✓
Important potential risks	Cardiac valvulopathy	✓	–	✓	–
	QT prolongation	✓	✓[3]	✓	-
	Off-label use	✓	✓[1]	✓	–
	Blood glucose disorder	✓	–	✓	–
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)	✓	✓[2,3]	✓	–
	Drug interactions	✓	✓[4]	✓	–

[1]Drug utilisation study
[2]Open label phase III clinical trial
[3]PASS
[4]Drug metabolism and drug interaction studies
Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;

- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Second round: New and outstanding recommendations

Recommendation 1: This is a new recommendation. The sponsor has provided justification to why QT prolongation should not be listed as a safety concern. Based on the available safety evidence provided by the sponsor, the evaluator considers that the clinical significance of QT interval increase caused by guanfacine alone is still uncertain. Therefore, it is acceptable that QT prolongation is not listed as an important potential risk in the ASA at this stage. However, it is recommended that risk minimisation to mitigate life threatening arrhythmia events caused by QT prolongation is strengthened for the following reasons:

- *Clinical trials*: although the QT prolongation caused by guanfacine in clinical trials did not lead to Torsades de pointes, patients with risk factors, for example, clinically significant ECG findings, history of cardiac abnormalities and medications affecting blood pressure or heart rate were excluded from the clinical trials (see EU-RMP for details).
- *Post-authorisation experience:* the post-authorisation adverse event cases quoted in the sponsor's response all had other contributing factors. However, an increased risk of serious adverse events cannot be dismissed when guanfacine is given to patients with other risk factors.
- *Product label*: the relevant content in the draft PI aligns with the product label approved by the US FDA. However, the European Medicines Agency (EMA) approved Summary of Product Characteristics (SmPC) provides more advice on monitoring and mitigating the risk:

  > *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…*
  >
  > *… Given the effect of Intuniv on heart rate, the concomitant use of Intuniv with QT prolonging medicinal products is generally not recommended.*

  It is recommended to the Delegate that the advice on monitoring for patients with risk factors and concomitant use of QT prolonging medication is included in the PI to improve patient safety.

Recommendation 2: This is a new recommendation. On 15 December 2016, the EMA published an assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006. The following comments are noted:

> *The data confirm what has been observed before in the trials, i.e. that Intuniv may induce weight gain and obesity. The US paediatric population is not considered a relevant reference population for this European study population.*

The SmPC already include a warning that weight increase /risk of obesity should be evaluated every 3 months in the first year of treatment, and every 6 months in the period thereafter. These data underscore the importance of this warning.

It is recommended that the Delegate considers the inclusion of the same warning against weight gain in the PI.

Recommendation 3: This is an outstanding recommendation from Recommendation 6 of the round 1 RMP evaluation report. The sponsor has stated that depression is a known adverse event that does not require further characterisation. Depression should be listed in the ASA as an 'Important identified risk' based on the following considerations and the sponsor's response:

- Depression can have an impact on the benefit-risk balance of guanfacine, which is used to treat ADHD.
- Both ADHD and depression can lead to suicidal ideation. In Australia, youth suicide caused by mental conditions is an important public health issue.

  Further, the EU approved SmPC contains the following advice:

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

  The approved EU Patient Information Leaflet contains the following advice:

  Talk to your doctor or pharmacist before taking this medicine if: you have thoughts or feelings of suicide

  It is recommended that the Delegate considers adding these advices to the PI and CMI to raise awareness and improve patient safety.

Recommendation 4: This is an outstanding recommendation from Recommendation 8 of the round 1 RMP evaluation report. The sponsor has differentiated 'intentional medication errors' from medication errors according to the EMA's definition. It provides adequate justification to why (unintended) medication errors should not be listed as a safety concern. This is acceptable. The sponsor has commented that the majority of intentional medication error cases reported non-serious adverse events. The sponsor should provide an analysis of the serious adverse events resulted from the intentional medication errors and assess the adequacy of the proposed risk minimisation based on the clinical consequences of intentionally not using Intuniv as recommended.

Recommendation 5: This is an outstanding recommendation from Recommendation 9 of the round 1 RMP evaluation report. The sponsor has proposed a drug utilisation study in Australia. The sponsor should provide the protocol for this study. This should include which electronic medical records databases the study will extract data from.

Recommendation 6: This is an outstanding recommendation from Recommendation 14 of the round 1 RMP evaluation report. The sponsor has proposed additional risk minimisation to mitigate all the important identified risks in the newly submitted ASA. This is satisfactory.

The sponsor should submit the draft educational materials to the TGA for review. The mock-up of proposed additional risk minimisation in Annex 11 of the EU-RMP is based on the indication and the product label approved in the EU. Of note, the checklist of contraindications appears to contain more conditions than the approved SmPC.

The sponsor should develop materials that reflect the authorised use and clinical practice in Australia. In particular, information regarding indication, contraindications, and precautions should align with the PI.

Wording for conditions of registration
Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

The EU-RMP version 1.5 dated 22 July 2015 (DLP 1 September 2013) (version, date, data lock point), with Australian Specific Annex version 1.0 dated 16 February 2017, to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Approval for registration of the proposed product can be recommended from a pharmaceutical chemistry and biopharmaceutic perspective.

Nonclinical

- There are significant deficiencies in the Module 4 data. However, this assessor does not consider them so serious as to preclude registration.
- The primary pharmacology studies support the treatment of childhood/juvenile ADHD with guanfacine.
- Secondary pharmacodynamics studies did not indicate likely off-target effects. Safety pharmacology studies showed that guanfacine can inhibit defecation in mice, have a diuretic effect in rats and dogs, and can produce bradycardia in dogs.
- Pharmacokinetic drug interaction studies did not indicate issues of concern for clinical use.
- Repeat-dose toxicity studies were largely based on the use of rodents. However, various results suggested that rodents are poor models for human use of guanfacine. An effect of guanfacine dosing on male fertility in dogs could be significant for clinical use.
- Guanfacine is not considered to pose a genotoxic or carcinogenic hazard.
- The proposed pregnancy Category (B3) is reasonable.
- There are no nonclinical objections to registration.
- The nonclinical evaluator proposed amendments to the draft Product Information (PI) document but these are beyond the scope of this AusPAR.

Clinical

Pharmacokinetics

Studies identified by the clinical evaluator [CE] as providing pharmacokinetic (PK) information (general PK, bioequivalence, special population, drug interactions and PopPK) in the submission are summarised in Table 5 above.

Summary of pharmacokinetics from the clinical evaluation report [CER]

- Guanfacine is absorbed from the gastrointestinal tract.
- The absolute bioavailability of guanfacine is 81%.
- No new bioavailability data of the tablet relative to an oral solution or micronised suspension were presented.
- The different extended release dosages (1mg, 2mg and 4 mg tablets) were found to be bioequivalent just as, both the clinical trial and market formulations were found to be bioequivalent. There was dose proportionality for AUC_{0-t} but not for C_{max} in the dose range 1 mg to 4 mg was found as the C_{max} increased to a lesser than expected extent from 1 mg to 2 mg. However, guanfacine 1 mg, 2 mg and 4 mg were dose proportional at steady state.
- PK in the target population (Study SPD503-107 Children and Adolescents with ADHD aged 7 to 16 years) demonstrated linear kinetics at steady state in the dose range 2 mg to 4 mg, and also between single dose and steady state for the 2 mg dose level. Age and gender differences in PK were attributed to differences in body weight.
- Food increased the AUC_{0-t} of a 4mg dose by 39% and C_{max} by 75%.
- Volume of distribution [Vd] was in the range of 823 to 894 L (about 6 L/kg), implying extensive tissue distribution.
- The mean plasma protein binding is 71.6% and is not influenced by plasma concentration or route of administration.
- Guanfacine is metabolised via CYP3A4/5 mediated oxidation, with subsequent phase II reactions of sulfation and glucuronidation. The major circulating metabolite is 3-Ohguanfacine sulphate. Guanfacine is primarily metabolised by the CYP3A4 isoenzyme. In vitro studies with human liver microsomes and recombinant CYP's demonstrated that guanfacine was primarily metabolized by CYP3A4.
- Metabolic clearance is hepatic. The major circulating metabolite is 3-OH-guanfacine sulphate
- The metabolites are excreted renally. The fraction of guanfacine excreted unchanged in the urine is approximately 36% of the ingested dose. Urine recovery after intravenous dosing was 50%. Renal clearance of guanfacine was 0.12 L/kg/hour). Renal clearance of guanfacine was 50% of total body clearance and appeared to be due to a net renal tubular secretory process. This secretory process appears to be mediated by OCT2 (a transport protein found in the kidney).
- The main covariates contributing to variability in CL (total clearance of drug from plasma) were weight and age. Race and sex were statistically significant but not clinically significant.
- In Study SPD503-113 clearance, scaled to body weight, decreased with increasing weight [but usually, parameters such as CL would be related to allometric scaling for

body weight (for example, weight$^{0.75}$)]. In that case, exposure correspondingly increased with increasing weight, reflecting the decreased CL.

- No data on neither impaired neither hepatic nor renal function.
- No data on genetic factors were included in the dossier but, the PK of guanfacine was similar in Japanese and Non-Hispanic Caucasian subjects
- In PopPK Study (SPD503-312) weight was the main predictor for guanfacine exposure, when scaled allometrically. Race and gender did not significantly affect guanfacine exposure.
- With regard to pharmacokinetic interactions:
  - Exposure to guanfacine was significantly increased by ketoconazole. At a 4 mg dose, the ratio (90% CI) exposed / unexposed for AUC_{0-t} was 278.59 (227.53 to 341.11) and for C_{max} was 174.54 (145.65 to 209.17).
  - Co-administration with rifampicin significantly decreased guanfacine AUC_{0-t} by 69% and C_{max} by 54%
  - There was also no effect of methylphenidate on guanfacine bioavailability and vice versa
  - Guanfacine and Lisdexamphetamine did not have any clinically significant effects upon the PK of each other

CE's overall conclusions on pharmacokinetics

- The pharmacokinetics of guanfacine have been adequately characterised
- Guanfacine in the extended release formulation (SPD503) has a favourable PK profile for use in children and adolescents with ADHD.

Pharmacodynamics

The CE stated that there were no new data in the dossier examining the primary pharmacology of guanfacine.

Summary of pharmacodynamics from the CER

- There were no new data on mechanism of action.
- With regard to the primary pharmacodynamic effect, the population PKPD study (Study SPD503-312) indicated that the guanfacine exposure response time course of ADHD-RS-IV scores was best describe by a linear drug effect proportional to the placebo response trajectory. The typical (95% CI) decrease in ADHD-RS-IV score, compared to placebo, was 37.1% (32.2% to 42.0%) per 0.1 mg of guanfacine exposure. The latter also best describes the relationship between drug concentration and its pharmacodynamic effects although there were no new data on time course of pharmacodynamic effects.
- As for the secondary pharmacodynamic effects, following up-titration of guanfacine dose to 4 mg daily, abrupt cessation did not result in rebound hypertension or other clinically significant adverse effects in comparison with tapered cessation (Study SPD503-102).

At doses were titrated up to 8 mg daily, there *was prolongation of QTcF to the threshold of regulatory concern, but there was no prolongation when QTc was calculated by QTcNi (Study SPD503-112).* The mean (90% CI) for difference guanfacine- placebo, change for baseline

in QTcF was 3.54 (0.78 to 6.29) at 6 hours post dose, and 7.61 (4.87 to 10.34) at 12 hours post dose. However, heart rate decreased by a mean of 20 bpm in the guanfacine group.

- The efficacy data did not indicate any gender or age related differences in PD response
- There were no new data on PD interactions.

CE's overall conclusions on pharmacodynamics

- In the dose range studied, the plasma concentration effect relationship was linear.
- There were no rebound effects on blood pressure with the extended release formulation.

Dosage selection

Studies identified by the CE as providing dosage selection information for the pivotal studies in the submission:

- PK and PD studies

These studies investigated the dose range from 1 mg to 8 mg per day in *adults.*

- Phase II studies

These studies examined the dose range 1 mg/day to 4 mg/day in the age range *6 to 17 years.*

- Phase III pivotal studies

The Phase III pivotal studies investigated the dose range of up to 4 mg/day in children aged 6 to 12 years and up to 7 mg/day in adolescents aged 13 to 17 years.

CE's overall conclusions on dose finding for the pivotal studies

- The sponsor has investigated tolerability, safety and efficacy in the dose range 1 mg to 7 mg per day.
- The final dosing used in the clinical trials was a weight-based dosing regimen that reflected the findings of the dose-finding studies. This weight-based dosing regimen supports the dosing recommendations in the Product Information document.

Efficacy

Studies identified by the CE as providing evaluable efficacy data in the submission

- Eight (8) pivotal or main efficacy studies conducted in children and adolescents with ADHD. Studies were performed as monotherapy and as co-medication with psychostimulants.
- One (1) study conducted in children and adolescents with ADHD and Oppositional Features.
- Five (5) supportive efficacy studies including two long-term follow-on studies.

Pivotal or main efficacy studies

Study SPD503-301

For details of study design see Attachment 2.

Primary efficacy outcome as per the CE:

- ADHD-RS-IV improved in a dose-related manner for all guanfacine groups compared to placebo. Mean (SD) change from baseline in ADHD-RS-IV was -15.40 (12.82) for guanfacine 2 mg, -15.79 (13.00) for 3 mg, -18.96 (13.71) for 4 mg and -8.86 (12.90) for placebo (p values all < 0.001).
- When analysed by weight adjusted dose, there was a more obvious dose-dependency in the change from baseline in ADHD-RS-IV total score. Efficacy was significantly greater than placebo in the younger age groups but not in the 13 to 17 years age group.
- Efficacy was demonstrated separately for ADHD-RS-IV total score for the combined type, but not for the inattentive type. However, efficacy was demonstrated for both inattentive and hyperactive/impulsivity subscales.

Other efficacy outcomes as per the CE:

- There was a significant improvement in CPRS-R total score overall and at all time points during the day
- There was a significant improvement in CTRS-R total score overall and at all time points during the school day
- A greater proportion of subjects treated with guanfacine had improvement in CGI-I: 47 (55.95%) subjects in the 2 mg group, 41 (50.0%) in the 3 mg, 45 (55.56%) in the 4 mg and 20 (25.64%) in the placebo
- A greater proportion of subjects treated with guanfacine had improvement PGA: 41 (62.12%) subjects in the 2 mg group, 31 (50.82%) in the 3 mg, 39 (66.10%) in the 4 mg and 15 (23.08%) in the placebo
- Consistent improvement in CHQ-PF50 was only seen at the 4 mg dose level
- There was a significant improvement in CHQ-CF87 only at the 4 mg dose level, and only for Family Activities: LS mean placebo adjusted difference (95% CI) 14.93 (2.89 to 26.98) p = 0.0108; and for Bodily Pain: -9.41 (-17.81 to 0.0236).

The CE commented that Study SPD503-301 demonstrated the dose range on an mg/kg basis that could be expected to have efficacy (linear response up to 0.17 mg/kg/day). The study maintenance phase was of too short a duration to establish efficacy (two weeks). Efficacy was not demonstrated for the inattentive subtype of ADHD.

Study SPD503-304

For study design details see Attachment 2.

The CE stated that the inclusion and exclusion criteria were essentially the same as for Study SPD503-301.

Primary efficacy outcome as per the CE:

- All the active treatment groups were superior to placebo in the reduction in ADHD-RS-IV score from baseline. The LS mean (95%) placebo adjusted difference was -6.75 (-11.3 to -2.2) for 1 mg, -5.41 (-9.9 to -0.9) for 2 mg, -7.31 (-11.8 to -2.8) for 3 mg and -7.88 (-12.3 to -3.4) for 4 mg. When analysed by weight adjusted dose, there was a clear dose effect relationship with greatest effect at the highest dose: 0.13 to 0.16 mg/kg/day.
- Efficacy was demonstrated in the 6 to 12 years age group but not in the 13 to 17 years age group.
- Efficacy was demonstrated by inattentive subscale scores.

- Efficacy was demonstrated by hyperactivity/impulsivity subscale scores.
- A subgroup analysis by ADHD type was not presented.

Other efficacy outcomes as per the CE:

- In comparison with placebo, there was a greater improvement in CPRS-R total score overall for all treatment groups. However, in the 2 mg group there were several time points when efficacy was not demonstrated: 4 hours, 12 hours and 14 hours post-dose.
- Clinical Global Impression-Severity (CGI-S) was not reported as an efficacy outcome.
- There was a significant improvement in CGI-I compared to placebo for the 1 mg, 3 mg and 4 mg dose groups but not for the 2 mg. Improvement in CGI was reported for 31 (54.4%) subjects in the 1 mg group, 27 (42.9%) in the 2 mg, 33 (55.0%) in the 3 mg, 35 (55.6%) in the 4 mg and 19 (30.2%) in the placebo.
- There was a significant improvement in PGA compared to placebo for the 1 mg, 3 mg and 4 mg dose groups but not for the 2 mg. Improvement in PGA was reported for 27 (50.9%) subjects in the 1 mg group, 20 (36.4%) in the 2 mg, 29 (61.7%) in the 3 mg, 30 (56.6%) in the 4 mg and 16 (30.2%) in the placebo.
- In comparison with placebo there was no consistent improvement in CHQ-PF50 scores for any active treatment group.

The CE commented that Study SPD503-304 confirmed the findings of Study SPD503-301. There was a clear linear relationship between dose and efficacy up to 0.16 mg/kg/day. The study maintenance phase was of too short a duration to demonstrate efficacy.

Study SPD503-307

For details of study design see Attachment 2.

Primary efficacy outcome as per the CE:

- There was a significant improvement in the oppositional subscale of CPRS-R: L in the guanfacine group compared to placebo. The LS mean change from baseline was -10.9 in the guanfacine group and -6.8 in the placebo, LS mean difference (95% CI) -4.1 (-6.1 to -2.1) $p < 0.001$. At endpoint there was a mean reduction of 56.2% in the guanfacine group and 33.7% in the placebo. At endpoint, there were 86 (67.2%) responders in the guanfacine group and 21 (28.4%) in the placebo, $p < 0.001$. In females, at endpoint the LS mean change from baseline was -12.4 in the guanfacine group and -5.1 in the placebo, $p < 0.001$.
- There was no difference in efficacy by race.
- A subgroup analysis was not presented by ADHD type.

Other efficacy outcomes as per the CE:

There was improvement in the guanfacine group compared to placebo for all secondary endpoints.

- For ADHD-RS-IV, at endpoint the LS mean change from baseline was -23.8 in the guanfacine group and -11.5 in the placebo, LS mean difference (95% CI) -12.3 (-16.1 to -8.5) $p < 0.001$. There was a 56.7% reduction in ADHD-RS-IV score in the guanfacine group and 26.5% reduction in the placebo.
- For CGI-I, at endpoint there was improvement in 93 (71.5%) subjects in the guanfacine group and 24 (32.0%) in the placebo, $p < 0.001$.
- For NYPRS-S, at endpoint the LS mean change from baseline was -16.0 in the guanfacine group and -9.6 in the placebo, LS mean difference (95% CI) -6.5 (-9.6 to -3.3) $p < 0.001$.

- For PSI/SF, at endpoint the LS mean change from baseline was 17.0 in the guanfacine group and 7.7 in the placebo, LS mean difference (95% CI) 9.2 (3.4 to 15.1) p < 0.001.
- For MSS a higher proportion of parents in the guanfacine group were satisfied with their child's behaviour, social interactions and attention while they were taking the medication; were happy with duration of effect but felt their child was sleepier during the day p< 0.001. Overall satisfaction was higher with guanfacine than placebo.

The CE commented that Study SPD503-307 demonstrated clinically and statistically significant improvement in oppositional features in children and adolescents aged 6 to 17 years with ADHD**.** The maintenance phase was of too short a duration to establish efficacy (3 weeks).

Study SPD503-312

For details of study design see Attachment 2.

Primary efficacy outcome as per the CE:

- There was a significant improvement in the primary efficacy outcome measure, ADHD-RS-IV, in the guanfacine group compared to placebo. The mean (SD) change (improvement) from baseline in the guanfacine group was -25.7 (10.09) and in the placebo was -19.5 (12.63), LS mean difference (95% CI) was -6.026 (-8.865 to -3.187) p < 0.001.
- Efficacy was not influenced by weight adjusted dose, sex or race.

Other efficacy outcomes as per the CE:

- For CGI-S, there were 78 (50.6%) subjects in the guanfacine group and 56 (36.1%) in the placebo who were normal or borderline mentally ill, p = 0.010
- CGI-I improved in 104 (67.5%) subjects in the guanfacine group and 71 (45.8%) in the placebo, p < 0.001.
- There was no significant difference between the treatment groups in WFIRS-P learning and school domain, family domain or global scores.
- There was no significant difference between the treatments groups in BRIEF-Parent Form, change from baseline.

The CE commented that Study SPD503-312 demonstrated efficacy in the 13 to 17 years age group. The primary efficacy outcome measure was ADHD-RS-IV which was also used in the inclusion criteria, was measured at baseline and the change from baseline to endpoint was analysed. The maintenance phase was of 6 weeks duration.

Study SPD503-313

For details of study design see Attachment 2.

Primary efficacy outcome as per the CE:

- Both guanfacine treatment groups had a greater improvement in ADHD-RS-IV score than placebo, but there was a slightly greater improvement in the PM group. The LS mean (95%) difference from placebo was -4.5 (-7.5 to -1.4) p = 0.002 in the AM group and -5.3 (-8.3 to -2.3) p < 0.001 in the PM group. There were 118 (79.2%) subjects coded as responders in the AM group, 123 (83.1%) in the PM group and 106 (69.7%) in the placebo.
- The effect size was similar for the subgroups of males and females, and by race.
- The effect size was also similar for inattentiveness and hyperactivity/impulsiveness subscales.

Other efficacy outcomes as per the CE:

- For CGI-I, there was improvement compared to placebo in both guanfacine groups: 105 (70.5%) subjects in the AM group, p = 0.024, 110 (74.2%) in the PM, p = 0.003 and 88 (57.9%) in the placebo.
- For CGI-S, there was significantly less severity in the guanfacine groups at endpoint.
- For Connor's Global Index – Parent (CGI-P), both guanfacine treatment groups had a greater improvement than placebo, but there was a slightly greater improvement in the PM group. The LS mean (95%) difference from placebo was -1.7 (-3.2 to –0.3) p = 0.019 in the AM group and -2.6 (-4.0 to -1.1) p < 0.001 in the PM group.
- For the Before-school Functioning Questionnaire (Wil-Hammer, BSFQ) there was similar benefit compared to placebo for both active treatment groups. The LS mean (95%) difference from placebo was -5.1 (-8.0 to –2.2) p < 0.001 in the AM group and -4.7 (-7.6 to -1.7) p = 0.002 in the PM group.
- For PGA, there was improvement compared to placebo in both guanfacine groups: 90 (69.8%) subjects in the AM group, p < 0.001, 90 (67.7%) in the PM, p < 0.001 and 67 (47.5%) in the placebo.
- For CPRS-R: L, both guanfacine treatment groups had a greater improvement than placebo, but there was a slightly greater improvement in the PM group. The LS mean (95%) difference from placebo was -2.4 (-3.9 to –0.9) p = 0.001 in the AM group and -2.2 (-3.6 to -0.7) p = 0.003 in the PM group.
- Post-Sleep Questionnaire there was no significant difference in quality of sleep between the treatment groups: mean (SD) change from baseline -6.6 (6.7) for AM, -6.3 (7.05) for PM and -4.2 (6.79) for placebo.

The CE commented that Study SPD503-313 indicates efficacy of guanfacine in subjects aged 6 to 17 years with ADHD and co-medicated with certain selected psychostimulants. The study maintenance phase was not of sufficient duration to demonstrate efficacy (3 weeks). The primary efficacy outcome measure was ADHD-RS-IV, which was used in the inclusion criteria and measured at baseline and endpoint. The study did not examine doses higher than 4 mg/day in subjects co-medicated with psychostimulants. There was no clinically significant difference between the morning and evening guanfacine extended release dosing.

Study SPD503-314

For details of study design see Attachment 2.

Primary efficacy outcome as per the CE:

- Both guanfacine groups were superior to placebo, with a similar effect size in the two guanfacine groups. The LS mean (95%) difference from placebo was -9.4 (-12.8 to -6.0) p < 0.001 in the AM group and -9.8 (-13.1 to -6.4) p < 0.001 in the PM group.
- There was a similar effect size for the subgroups of sex, race and presence of ODD.
- Improvement was demonstrated for guanfacine relative to placebo for both hyperactivity/impulsivity and inattentive subscores. There were 65 (62.5%) subjects coded as responders in the AM group, 67 (60.4%) in the PM group and 34 (30.9%) in the placebo.

Other efficacy outcomes as per the CE:

- For CGI-I, there was improvement in 69 (66.3%) subjects in the AM group, p < 0.001, 75 (67.0%) in the PM, p < 0.001, and 35 (31.8%) in the placebo.

- For CGI-S, there was lesser severity at endpoint in both of the guanfacine groups. CGI-S category 1 or 2 was recorded for 33 (31.7%) subjects in the AM group, 41 (36.6%) in the PM and 14 (12.7%) in the placebo.
- For CPRS-R: S, there was significant improvement in both guanfacine groups relative to placebo. The LS mean (95%) difference from placebo was -12.5 (-17.8 to -7.3) $p < 0.001$ in the AM group and -10.8 (-16.0 to -5.6) $p < 0.001$ in the PM group. There was a similar effect size for both morning and evening assessments. There was improvement in the CPRS-R: S cognitive problems subscale: the LS mean (95%) difference from placebo was -2.7 (-4.2 to -1.2) $p < 0.001$ in the AM group and -2.7 (-4.1 to -1.2) $p < 0.001$ in the PM group.
- There was no significant difference between the treatment groups in HUI2/3.
- For WFIRS-P, there was significant improvement in both guanfacine groups relative to placebo. The LS mean (95%) difference from placebo was -0.15 (-0.26 to -0.05) $p = 0.004$ in the AM group and -0.18 (-0.28 to -0.07) $p = 0.001$ in the PM group.
- There was no significant difference between guanfacine and placebo for Bedtime Resistance subscale of the CSHQ.
- At endpoint, there was no significant difference between guanfacine and placebo for PSQ.

The CE commented that in Study SPD503-314, there was no clinically significant difference in efficacy between morning and evening doses. The maintenance phase was of too short a duration to establish efficacy (5 weeks). The primary efficacy outcome measure was ADHD-RS-IV, which was used in the inclusion criteria and measured at baseline and endpoint.

Study SPD503-315

For details of study design see Attachment 2.

Primary efficacy outcome as per the CE:

- The ADHD-RS-IV score decreased to a lesser extent in the guanfacine group compared to placebo: LS mean difference (95% CI) -6.24 (-9.01 to -3.48) $p < 0.001$. Efficacy was demonstrated for both the hyperactivity/impulsivity and inattentiveness subscores.
- For CGI-S, 75 (50.0%) subjects in the guanfacine group and 49 (32.5%) in the placebo were normal/borderline mentally ill, $p = 0.001$.

Other efficacy outcomes as per the CE:

- At end of study, there was no significant difference between the treatment groups in WFIRS-P, except for the learning and school domain score which was superior for the guanfacine group: LS mean (SE) 0.37 (0.056) for guanfacine and 0.23 (0.078) for placebo, $p = 0.030$.
- There was no significant difference between the treatment groups in HUI-2/3.

The CE commented that Study SPD503-315 demonstrated efficacy for guanfacine in children and adolescents aged 6 to 17 years with ADHD. The maintenance phase was of sufficient duration (6 weeks). The study demonstrated maintenance of efficacy for 26 weeks. The primary efficacy outcome measure was ADHD-RS-IV, which was used in the inclusion criteria and measured at baseline and endpoint. The benefits were primarily for symptomatic scores (ADHD-RS-IV) but benefit was also demonstrated for some functioning scores (WFIRS-P learning and school domain score). There was no significant difference in quality of life scores (HUI-2/3).

Study SPD503-316

For details of study design see Attachment 2.

Primary efficacy outcome as per the CE:

- Both guanfacine extended release and atomoxetine were superior to placebo, with similar effect sizes. The mean (SD) change from baseline in ADHD-RS-IV was -23.9 (12.41) for guanfacine, -15.0 (13.07) for placebo and -18.6 (11.91) for atomoxetine. The LS mean difference (95% CI) to placebo was -8.9 (-11.9 to -5.8) $p < 0.001$ for guanfacine and -3.8 (-6.8 to -0.7) $p = 0.017$ for atomoxetine.
- Similar efficacy was demonstrated for both the hyperactivity/impulsiveness and inattentive subscales.
- The sensitivity analysis did not have a significant effect on the results.

Other efficacy outcomes as per the CE:

- At endpoint, CGI-S was normal/borderline mentally ill for 42 (37.5%) in the guanfacine extended release group, 28 (25.2%) in the placebo group and 29 (25.9%) in the atomoxetine group.
- There was improvement in CGI-I for 76 (67.9%) subjects in the guanfacine group, 49 (44.1%) in the placebo and 63 (56.3%) in the atomoxetine. The difference (95% CI) for the % subjects with improvement from placebo was 23.7 (11.1 to 36.4) %, $p < 0.001$ for guanfacine and 12.1 (-0.9 to 25.1) %, $p = 0.024$ for atomoxetine.
- The mean (SD) change from baseline in WFIRS-P Learning and School Domain scores was -0.610 (0.6695) for guanfacine, -0.378 (0.5489) for placebo and -0.571 (0.6367) for atomoxetine. The LS mean difference (95% CI) to placebo was -0.217 (-0.358 to -0.076), $p = 0.003$ for guanfacine and -0.162 (-0.305 to -0.019), $p = 0.026$ for atomoxetine.
- The mean (SD) change from baseline in WFIRS-P Family Domain scores was -0.596 (0.7706) for guanfacine, -0.507 (0.6893) for placebo and -0.571 (0.6367) for atomoxetine. The LS mean difference (95% CI) to placebo was -0.209 (-0.358 to -0.059), $p = 0.006$ for guanfacine and -0.090 (-0.241 to 0.061), $p = 0.242$ for atomoxetine.
- The mean (SD) change from baseline in WFIRS-P Global scores was -0.486 (0.5012) for guanfacine, -0.300 (0.3745) for placebo and -0.423 (0.4220) for atomoxetine. The LS mean difference (95% CI) to placebo was -0.165 (-0.266 to -0.064), $p = 0.001$ for guanfacine and -0.104 (-0.207 to -0.001), $p = 0.048$ for atomoxetine.
- There was no significant difference between the treatment groups in HUI-2/3 scores.

The CE commented that Study SPD503-316 demonstrated efficacy for guanfacine extended release in comparison with placebo in children and adolescents aged 6 to 17 years with ADHD. Efficacy was demonstrated for the symptomatic score of ADHD-RS-IV and the functional scores of WFIRS-P Global score, Learning and School Domain score and Family Domain score. No formal comparisons of either superiority or non-inferiority were performed in comparison with atomoxetine. Hence, no formal conclusions can be made with regard to efficacy in comparison with atomoxetine.

Other efficacy studies

SPD503-202

For details of study design see Attachment 2.

Efficacy outcome:

- There was improvement in SKAMP deportment scores relative to placebo in the guanfacine group but not in attention scores.
- PERMP scores improved in the guanfacine group relative to placebo.
- More subjects in the guanfacine group had improvement in CGI improvement scores but this was not statistically significant.

SPD503-205

For details of study design see Attachment 2.

Efficacy outcome:

- The mean (SD) change from baseline in ADHD-RS-IV score was -17.8 (10.20), $p < 0.0001$, in the methylphenidate group and -13.8 (11.19), $p < 0.0001$, in the amphetamine.
- The mean (SD) change from baseline in CPRS-R score was -22.18 (15.47), $p < 0.0001$, in the methylphenidate group and -16.28 (18.12), $p = 0.0002$, in the amphetamine.
- Improvement in CGI-I occurred for 28 (77.8%) subjects in the methylphenidate group and 18 (66.7%) in the amphetamine.
- Improvement in PGA score occurred for 32 (88.9%) subjects in the methylphenidate group and 21 (77.8%) in the amphetamine.
- There was no significant change in CHQ-PF-50 Physical Summary Score. The mean (SD) change from baseline in CHQ-PF-50 Psychosocial Summary Score was 8.98 (6.69), $p < 0.0001$, in the methylphenidate group and 11.56 (10.00), $p < 0.0001$, in the amphetamine.

Study SPD503-206

For details of study design see Attachment 2.

Efficacy outcomes:

For the *cognitive* assessments:

- There was no significant difference between the treatment groups in CRT: LS mean difference (95% CI), placebo – guanfacine, 2.2 (-16.3 to 20.7).
- There was no significant difference between the treatment groups in the change from baseline in reaction time for correct responses: mean change (SD) 20.2 (59.77) msec for guanfacine and 21.8 (58.09) msec for placebo.
- There was no significant difference between the treatment groups in the change from baseline in movement time: mean change (SD) 19.4 (74.27) msec for guanfacine and 8.8 (84.00) msec for placebo, $p = 0.302$.
- There was no significant difference between the treatment groups in the change from baseline in CRT total time: mean change (SD) 40.1 (114.34) msec for guanfacine and 30.7 (110.72) msec for placebo, $p = 0.723$.
- There was no significant difference between the treatment groups in the change from baseline in CRT accuracy: mean change (SD) 0.1 (1.22) for guanfacine and 0.1 (1.17) seconds for placebo, $p = 0.980$.
- There was no significant difference between the groups in SWM.

- There was no significant difference between the treatment groups in the change from baseline in DSST: mean change (SD) 18.3 (14.03) for guanfacine and 20.7 (17.18) seconds for placebo, p = 0.274.
- There was no significant difference between the treatment groups in the change from baseline in PERMP score: mean change (SD) 38.7 (74.80) for guanfacine and 17.2 (83.60) seconds for placebo, p = 0.151.

For the *efficacy* assessments:

- There was a statistically significant improvement in ADHD-RS-IV in the guanfacine group compared with placebo: mean change (SD) -18.0 (10.72) for guanfacine and -11.9 (13.12) for placebo, p = 0.001.
- There was a statistically significant improvement in ADHD-RS-IV subscale score in the guanfacine group compared with placebo: mean change (SD) -8.8 (5.98) for guanfacine and -5.5 (7.23) for placebo, p = 0.001.
- There was a statistically significant improvement in ADHD-RS-IV hyperactivity / impulsivity subscale in the guanfacine group compared with placebo: mean change (SD) -9.2 (5.83) for guanfacine and -6.5 (6.68) for placebo, p = 0.002.
- A significantly greater proportion of subjects in the guanfacine group had improvement in CGI-I: 67(56.8%) in the guanfacine group and 20 (35.1%) in the placebo, p = 0.007.

Study SPD503-303

For details of study design see Attachment 2.

Efficacy outcomes:

- For ADHD-RS-IV, efficacy was maintained to endpoint for all three dose levels (prior to tapering): mean (SD) change from baseline -18.1 (13.38) for 2 mg, -17.6 (12.60) for 3 mg and -18.4 (13.13) for 4 mg (p < 0.001).
- At endpoint, 95 (58.6%) subjects had demonstrated improvement in PGA.
- There was no significant change from baseline in CHQ-PF50 physical summary scores.
- There was a significant improvement from baseline in CHQ-PF50 psychosocial summary score: mean (SD) change from baseline 12.3 (12.35) p < 0.001.
- An analysis of CHQ-CF87 was not reported.

Study SPD503-305

For details of study design see Attachment 2.

Efficacy outcomes:

- For ADHD-RS-IV efficacy was maintained to endpoint for all four dose levels (prior to tapering): mean (SD) change from baseline -23.8 (12.30) for 1 mg, -22.5 (12.25) for 2 mg, -20.0 (13.95) for 3 mg and -18.4 (13.73) for 4 mg (p < 0.001).
- For CPRS-R efficacy was maintained to endpoint for all four dose levels (prior to tapering): mean (SD) change from baseline -17.4 (21.60) for 1 mg, -19.9 (17.53) for 2 mg, -20.3 (16.84) for 3 mg and -15.7 (21.79) for 4 mg (p < 0.001).
- For CGI-I at endpoint, 63 (29.3%) subjects were very much improved, 62 (28.8%) were much improved and 48 (22.3%) were minimally improved.
- For PGA at endpoint, 32 (15.2%) subjects were very much improved, 94 (44.5%) were much improved and 52 (24.6%) were minimally improved.

- There was no significant change in CHQ-PF50 physical summary.
- CHQ-PF50 psychosocial summary improved by a mean (SD) of 9.2 (11.91) $p < 0.001$.

The CE commented on other efficacy studies that the long term follow-on Studies SPD503-303 and SPD503-305, supported maintenance of efficacy through to 24 months. Study SPD503-206 indicated that guanfacine did not have a significant effect on cognitive scores.

Analyses performed across trials; pooled and Meta- analyses

In a pooled analysis of Study SPD503-316 and Study SPD503-312, there was significant improvement in all the domains of the WFIRS-P with the exception of Child Self-concept and Risk.

The CE's conclusions on clinical efficacy

- The pivotal studies have demonstrated efficacy in comparison with placebo for guanfacine extended release tablet, in subjects with ADHD aged 6 to 17 years.
- Study SPD503-312, Study SPD503-315 and Study SPD503-316 all had a maintenance phase ≥ 6 weeks in duration. The studies used outcome measures for both symptomatic and functional domains. The primary efficacy outcome measure was ADHD-RS-IV which was used for inclusion and for efficacy. SPD503-315 used a responder category that was based on ADHD-RS-IV and GCI-S.
- In a pooled analysis of Study SPD503-316 and Study SPD503-312, there was significant improvement in all the domains of the functional score WFIRS-P with the exception of Child Self-concept and Risk.
- Efficacy was demonstrated for oppositional symptoms in subjects with ADHD with oppositional symptoms in Study SPD503-307.
- A linear dose-response up to 0.17 mg/kg/day was demonstrated in Study SPD503-301 and Study SPD503-304.
- There is support for maintenance of efficacy for up to 24 months. Although Study SPD503-315 went for 26 weeks, Study SPD503-303 and Study SPD503-305 were supportive of efficacy for up to 2 years.
- There was no significant difference in efficacy between morning and evening dosing of guanfacine in Study SPD503-313 and Study SPD503-314.
- Efficacy is supported in subjects with ADHD who are also taking psychostimulants. The dose of guanfacine tested in the study (Study SPD503-313) was up to 4 mg daily. This is less than the maximum dose in comparable age groups (up to 7 mg/day in the 13 to 17 years age group).
- Efficacy was not demonstrated separately for the inattentive subtype of ADHD. A subgroup analysis was performed in Study SPD503-301 but not in subsequent studies. This subgroup analysis did not show efficacy in the subgroup of subjects with inattentive type ADHD.
- Improvement in quality of life scores (HUI-2/3) was not demonstrated in any of the clinical studies.
- There were no comparator controlled studies. In Study SPD503-316 a group treated with atomoxetine was included to provide 'reference data' but no formal comparison of efficacy was either planned or conducted. However in that study, the effect sizes of guanfacine and atomoxetine were comparable.
- There is no evidence of efficacy in subjects with comorbid conditions including: any severe comorbid Axis II disorders or severe Axis I disorders such as post-traumatic

stress disorder, bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder, substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis, or conduct disorder. Subjects with these comorbid conditions were excluded from the pivotal studies.

- The outcome measures used in the pivotal studies were a combination of symptomatic and functional scores. Symptomatic scores such as ADHD-RS-IV, CPRS-R, CTRS-R, CGI-I and PGA measured changes in ADHD symptomatology and indicated benefit for guanfacine. NYPRS-S and CPRS-R: L measured oppositional symptomatology and also indicted benefit. The results for the functional score WFIRS-P indicate benefit that became more apparent on the pooled analysis of Study SPD503-316 and Study SPD503-312. Quality of life outcome measures, such as CHQ-PF50, CHQ-CF87 and HUI-2/3 did not demonstrate benefit for guanfacine. All of these outcome measures have been appropriately validated and are acceptable outcome measures for children and adolescents with ADHD.
- The pivotal studies were well designed. The outcome measures were appropriate. The inclusion criteria, whilst restrictive, still represent the general population of children and adolescents with ADHD in Australia. The studies were adequately powered. The statistical techniques were appropriate. There were adequate measures taken to account for multiplicity. There were few dropouts during the study and few subjects excluded from analysis.
- The dosing regimen proposed by the sponsor in the draft PI document is supported by the pivotal studies. This is a weight based dosing regimen, which was used in the pivotal studies.

Regarding the overall conclusions on clinical safety, the CE stated that

- In the submitted data, overall exposure to guanfacine extended release (SPD503) was 2411 subjects, with 1,718 subjects aged 6 to 12 years and 693 subjects aged 13 to 17 years at the time of randomisation. There were 482 subjects exposed for ≥ 180 days, 235 subjects exposed for ≥ 360 days and 101 subjects exposed for > 720 days. Subjects were exposed to up to 7 mg/day and up to 0.16 mg/kg/day. In the post-marketing data, a total of 3,243 subjects had been treated with SPD503 in clinical trials and the estimated cumulative worldwide patient exposure was 965,432 patient years of treatment.
- Overall, the rate of TEAEs was higher in the guanfacine extended release group than in the placebo [2046 (84.9%) guanfacine subjects compared with 620 (63.7%) placebo subjects]. In the guanfacine group, there were 1,467 (85.4%) subjects aged 6 to 12 years and 579 (83.5%) subjects aged 13 to 17 years with TEAEs. In the guanfacine group, there was a higher rate of somnolence, headache, fatigue and sedation (regardless of dose or age group) compared to placebo
- Overall, *the rate of treatment related* TEAEs {TR-TEAEs} was higher in the guanfacine extended release group than in the placebo [1765 (73.2%) guanfacine subjects compared with 357 (36.7%) placebo subjects]. In the guanfacine group, there were 1,275 (74.2%) subjects aged 6 to 12 years and 490 (70.7%) subjects aged 13 to 17 years with TR-TEAEs. Somnolence, sedation and headache were the most common TR-TEAEs.
- There were no deaths in the study program.
- Overall, the rate of SAEs was higher in the guanfacine extended release group than in the placebo [49 (2.0%) guanfacine subjects compared with 8 (0.8%) placebo subjects]. In the guanfacine group, there were 33 (1.9%) subjects aged 6 to 12 years and 16 (2.3%) aged 13 to 17 years with SAEs. Syncope and sedation were the most common SAEs in the guanfacine group.

- Overall, the rate of DAE was higher in the guanfacine extended release group than in the placebo [261 (10.8%) guanfacine subjects compared with 13 (1.3%) placebo subjects]. In the guanfacine group, there were 200 (11.6%) subjects aged 6 to 12 years and 61 (8.8%) aged 13 to 17 years with DAE. Somnolence and syncope were the commonest reasons for DAE in the guanfacine group.
- At doses titrated up to 8 mg, there was prolongation of QTcF to the threshold of regulatory concern, but there was no prolongation when QTc was calculated by QTcNi (Study SPD503-112). The mean (90% CI) for guanfacine-placebo difference change from baseline, in QTcF was 3.54 (0.78 to 6.29) at 6 hours post dose and 7.61 (4.87 to 10.34) at 12 hours post dose. However, heart rate decreased by a mean of 20 bpm in the guanfacine group. Subsequently, ECG data were collected for all of the Phase III and Phase II studies and no significant concerns with regard to QTc prolongation were identified in these data. Of note, subjects with known QTc prolongation or who were taking drugs known to prolong QTc were excluded from all of these studies.
- HR, SBP and DBP decreased from the first dose of guanfacine and normalised over several months of treatment. With tapered withdrawal of guanfacine, rebound hypertension was not clinically significant. Postural hypotension and syncope was reported in patients treated with guanfacine. The pivotal trials excluded subjects with hypertension or orthostatic hypotension.
- Somnolence and sedation were common adverse events. The rate of somnolence/sedation increased with dose in the fixed dose studies, but a dose effect was not apparent in the dose optimisation studies.
- Adverse psychiatric changes were not identified as a safety issue. There was no apparent increase in suicidality with guanfacine.
- The pivotal clinical trials excluded patients with a broad range of comorbidities and the dossier does not contain safety data for use in these patients. Typical exclusion criteria used in the development program were those from Study SPD503-313:
  - Any current, controlled (requiring a prohibited medication or behavioural modification program) or uncontrolled, co-morbid psychiatric diagnosis (except ODD), including any severe co-morbid Axis II disorders or severe Axis I disorders such as Post Traumatic Stress Disorder (PTSD), bipolar illness, psychosis, pervasive developmental disorder, obsessive-compulsive disorder (OCD), substance abuse disorder, or other symptomatic manifestations or lifetime history of bipolar illness, psychosis or conduct disorder that, in the opinion of the Investigator, contraindicate SPD503 treatment or confound efficacy or safety assessments.
  - Subjects who are at suicide risk, any subject who has previously made a suicide attempt or those who are currently demonstrating active suicide ideation.
  - Subject has a history of seizure disorder (other than a single childhood febrile seizure occurring before the age of 3 years).
  - History or presence of known structural cardiac abnormalities, symptomatic cardiovascular disease, advanced arteriosclerosis, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, syncope, cardiac conduction problems (for example, clinically significant heart block or clinically significant abnormality in QT or QTc interval and so on), exercise related cardiac events including syncope and pre-syncope, clinically significant bradycardia or any other serious cardiac problem that may place a subject at increased vulnerability to the effects of a stimulant and/or α2-agonist medication.
  - Subject has a family history of sudden cardiac death or ventricular arrhythmia.

- Subject has symptomatic or clinically meaningful orthostatic hypotension based on clinical judgment.
- History of controlled or uncontrolled hypertension.
- Current use of any prohibited medication or other medications, including herbal supplements that have CNS effects or affect cognitive performance, such as sedating antihistamines and decongestant sympathomimetics (bronchodilators are permitted).
- Current use of any medication including herbal supplements that affect BP or HR or are known to prolong the QT/QTc interval (excluding the subject's current ADHD medication).
- Morbidly overweight or obese, as defined by a BMI > 95th percentile.
- Weight less than 55 lbs (25kg).
- Weight greater than 176 lbs (80kg).
- Pregnancy or currently lactating.
- History of alcohol or other substance abuse or dependence, as defined by DSM-IV (with the exceptions of caffeine or nicotine) within the last year.

The CE commented that the above exclusion criteria and the conditions they represent should be mentioned in the contraindications and warnings sections of the PI document.

Recommendation regarding authorisation as per the CE (second round)

The application for Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, 3 mg and 4 mg modified release tablets should be rejected for the following indication:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive)*

The reason for rejection is that Intuniv (guanfacine hydrochloride) has not been compared with currently approved treatments for ADHD, and therefore its place in the order of management of the condition is unknown.

Consideration could be given for approval of the following alternative indication:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) where psychostimulants, atomoxetine and/or behavioural treatments have been ineffective or are contraindicated*

Risk management plan

See Pharmacovigilance section above.

Risk-benefit analysis

Delegate's considerations

The submitted data point to the approvability of guanfacine extended release tablet [Intuniv].

The CE has rejected the sponsor's proposed indication and considers a modified indication for approval:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) where psychostimulants, atomoxetine and/or behavioural treatments have been ineffective or are contraindicated.*

Given the proposed dosage instruction and the current contemporary medical management of ADHD, the Delegate believes that the sponsor's proposed indication requires additional modification to:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) without or with (as adjuvant to) psychostimulants or atomoxetine. Use of Intuniv should incorporate the standard comprehensive management programme [psycho-social and educational measures] for ADHD.*

The latter is akin to both the EU and Canadian indications.

There are some benefit-risk balance issues regarding the use of Intuniv (guanfacine hydrochloride) 1 mg, 2 mg, 3 mg and 4 mg modified release tablets. Those issues need to be ameliorated for the benefit-risk balance to become favourable. The risks are listed below for inclusion under the Contraindication section of the draft PI.

- Use in doses above 4 mg in patients also treated with psychostimulants.
- Use in patients operating heavy equipment or driving
- Use in patients with a history of long QT syndromes
- Use in patients co-medication with drugs known to prolong the QTc interval

The sponsor was initially advised about the promotional content of its proposed trade name 'Intuniv', that is, the implicit suggestion that guanfacine will or can '*Intune, Finetune*' all aspects of the proposed indication→ADHD. It was argued by the sponsor that other regulatory agencies have no such concern.

The quality evaluator stated that approval cannot be recommended from the pharmaceutical chemistry perspective until outstanding issues are resolved.

The nonclinical evaluator stated that there are significant deficiencies in the Module 4 data. However, this assessor does not consider them so serious as to preclude registration. Modifications to the draft PI are suggested.

The RMP evaluator has made additional amendment to the draft PI.

Having evaluated the gamut of clinical data provided, the CE has rejected the sponsor's proposed indication. The reason being that Intuniv (guanfacine hydrochloride), has not been compared with currently approved treatments for ADHD, and therefore its place in the order of management of the condition is unknown. On that basis the CE considered a modified indication for approval:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) where psychostimulants, atomoxetine and/or behavioural treatments have been ineffective or are contraindicated.*

Given the proposed dosage instruction and the current contemporary medical management of ADHD, the delegate believes that the sponsor's proposed indication requires additional modification to:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) without or with (as adjuvant to) psychostimulants or atomoxetine. Use of Intuniv*

should incorporate the standard comprehensive management programme [psycho-social and educational measures] for ADHD.

The latter is akin to both the EU and Canadian indications.

Proposed action

Based on the available evidence from the evaluated submitted data, the Delegate was inclined at this stage to favour the approval of the application subject to resolving issues arising from the ACM deliberations and finalising matters pertaining to the

(i) quality data and
(ii) suggested modifications to the draft PI as per the nonclinical, clinical and RMP evaluators

to the satisfaction of the TGA.

Request for ACPM advice

1. Consideration of the Delegate's additional modifications to the sponsor's proposed indication
2. Acceptability of the proposed trade name Intuniv
3. Absolute approval is dependent on satisfactorily resolving outstanding quality pharmaceutical issues

Response from Sponsor

The sponsor appreciates the opportunity to provide a response to address some issues raised in the Delegate's Overview.

Intuniv (guanfacine HCl) is a selective alpha2A-adrenergic receptor agonist. Guanfacine is not a CNS stimulant, a monoamine transporter inhibitor or releaser of pre-synaptic dopamine or norepinephrine. The sponsor considers the application for registration comprises a body of clinical evidence that supports the safety and efficacy of guanfacine in patients with ADHD.

Intuniv has received marketing approval for ADHD in Canada, EU, USA and Japan. The Delegate has asked the ACM for advice on the following matters:

1. Consideration of the delegate's additional modifications to the sponsor's proposed indication
2. Acceptability of the proposed trade name: Intuniv
3. Absolute approval is dependent on satisfactorily resolving outstanding Module 3 pharmaceutical issues

Proposed indication

Following two rounds of TGA evaluation and the sponsor's responses to the evaluation reports, the Delegate has proposed the following modified indication statement:

Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) without or with (as adjuvant to) psychostimulants or atomoxetine.

Use of Intuniv should incorporate the standard comprehensive management programme [psycho-social and educational measures] for ADHD.

Because clinical trials with guanfacine have not been conducted using adjunctive treatment with atomoxetine, there are currently no efficacy and safety data to support the

use of guanfacine as an adjunctive therapy to atomoxetine. The sponsor proposes the following slightly modified indication statement:

> *Intuniv is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) without or with (as adjuvant to) psychostimulants.*
>
> *Use of Intuniv should incorporate the standard comprehensive management programme [psycho-social and educational measures] for ADHD.*

Proposed trade name: Intuniv

As mentioned in the sponsor's response to the second round evaluation, the request for an alternative tradename is confusing because the concerns of the agency were not raised during prior clinical or RMP evaluations. The proposed tradename Intuniv was found to be acceptable by other comparable regulatory agencies in the EU, USA, Japan and Canada, jurisdictions where a robust tradename review process is undertaken, using criteria such as the FDA's document 'How FDA Reviews Proposed Drug Names'.[19]

Furthermore, given the proposed scheduling for Intuniv is S4 – Prescription Medicine, it will not be directed to consumer level promotional activities. The prescribers are well informed and make decisions based on the efficacy and safety data within the PI document rather than merely based on the tradename.

Outstanding quality pharmaceutical issues

The 16 questions posed in the body of the quality report were answered in the response to second round questions on the 20 April 2017 as per TGA timescales.

The sponsor acknowledges the TGA's email dated 8 May 2017 identifying the forced degradation studies, an official finished product specification, and bioanalytical validation results as remaining quality outstanding issues. The sponsor is committed to working with TGA to submit required information to support timely resolution of these outstanding issues. In accordance with feedback received from TGA, the sponsor will work with the TGA should a mutual clock stop be necessary. The sponsor proposes the following:

Questions 5 and 11

The forced degradation study review is underway and the sponsor confirms final data, including mass balance, will be available the week of 19 June 2017, as has been previously committed.

Question 13

As the TGA has accepted the sponsor's proposed specifications, the official finished product specification is being created and will be submitted upon finished product manufacturer's and the sponsor's internal approval process. The specification is anticipated to be available the week of 22 May 2017.

Question 15

The TGA has requested further revalidation data for specificity of bioanalytical method used in evaluation of effect of concomitant medications. Upon TGA's request, the bioanalytical method revalidation activities were initiated and will be expedited. However, due to the timeline for data generation the report is estimated to be completed in July 2017. The sponsor is working with TGA to evaluate whether a proposal to submit post approval commitment would be acceptable.

[19] https://www.fda.gov/downloads/drugs/drugsafety/medicationerrors/ucm080867.pdf

Contraindications

All four contraindications suggested during the second round were addressed in the responses dated 07 April 2017.

Use in doses above 4 mg in patients also treated with psychostimulants

As suggested in the second round response, guanfacine at doses up to 4 mg has been shown to provide added efficacy as an adjunctive therapy in patients who were suboptimal to psychostimulant treatment alone. Guanfacine is proposed to be dosed based upon body weight (mg/kg) and the same therapeutic dose (and associated similar plasma concentration), such as 0.08 mg/kg, could be achieved by 4 mg in a low weight patient (50 kg) or by a dose higher than 4 mg, such as 5 mg in a high weight patient (62.5 kg). Even though doses above 4 mg have not been evaluated in patients treated with psychostimulants, no contraindication was found at the weight based therapeutic dose range using doses up to 4 mg. Therefore, the sponsor maintains the position that, rather than a contraindication, the following wording is suggested in this context to reflect the true fact in the clinical development program *Doses above 4 mg/day have not been studied in co-administration trials in children and adolescents, so are not recommended*.

Use in patients operating heavy equipment or driving

The sponsor's response to the Delegate's concern regarding guanfacine and 'Use in patients operating heavy equipment or driving' in the second round included a discussion of the data and the empirical use. The key information presented in the response includes: i) patients with ADHD can have deficits in attention, executive function, and spatial abilities that can contribute to compromised outcomes when driving and/or operating machinery; ii) pharmacological treatment can be beneficial and risk-reducing in these patients; iii) Impairments in various cognitive function have been associated with the driving difficulty and cognitive assessments including visual perception and visual spatial ability, attention, processing speed, and executive function are imperative for determining an individual's capacity to drive safely; iv) in cognitive assessments in Study SPD503-206, guanfacine treatment revealed no cognitive impairment in patients with ADHD measured objectively by the CANTAB tests[20] including 5-point Choice Reaction Time (CRT) assessing reaction time, reaction time for correct response and CRT accuracy, and spatial working memory.

In addition, contraindication statements relating to use in patients when driving and/or operating machinery do not exist in other labels for similar drugs, such as clonidine, within the same class. Based on the available scientific data, no direct evidence has been found to associate guanfacine with increased risk of driving and operating heavy equipment. Due to the dizziness and sedative events observed in some patients when starting treatment with guanfacine and that are in most cases self-limiting, the sponsor proposes to add caution and warning statements, rather than a contraindication, which is consistent with α 2- adrenergic receptor agonist class labeling for patients who drive and/or operating machinery during the first few weeks of guanfacine treatment. A further revised text under 'Precautions - Effect on Ability to Drive and Use Machines' section of the proposed PI is provided with this response.

Use in patients with a history of long QT syndromes

Use in patients co-medication with drugs known to prolong the QTc interval

Although the updated safety topic report on long QT syndrome and QT prolongation summarises a review of a larger data pool than that included in the 2014 report, the

[20] The Cambridge Neuropsychological Test Automated Battery (CANTAB) originally developed at the University of Cambridge in the 1980s is a computer-based cognitive assessment system consisting of a battery of neuropsychological tests, administered to subjects using a touch screen computer.

conclusions remain the same: no evidence has been observed of a causal link between guanfacine and QT prolongation.

Accordingly, contraindication statements in line with that which has been requested are not included in the core company data sheet and should not be included in the marketing application for Australia.

Should the TGA continue to request these two contraindications as a drug class requirement, then the sponsor will consent to include these and corresponding statements in the PI and CMI.

Advisory Committee Considerations

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Intuniv modified release tablets containing 1 mg, 2 mg, 3 mg and 4 mg of guanfacine hydrochloride to have an overall positive benefit-risk profile for the delegate's amended indication:

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

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

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA
- modifications to the draft PI as per Modules 4 and 5 to the satisfaction of TGA
- resolution of Module 3 data to the satisfaction of TGA
- negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and specifically advised on further modifications to include the following:

- Amendment of the PI to reflect the ACM wording as written in the resolution outcomes.

Specific Advice

The ACM advised the following in response to the Delegate's specific questions on the submission:

1. *Consideration of the Delegate's additional modifications to the sponsor's proposed indication*

The ACM is in agreement with the Delegate to further modify the Delegate's proposed indication with the following wording:

> *For the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old, as monotherapy (when stimulants or atomoxetine are not*

suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants).

2. *Acceptability of the proposed trade name: Intuniv*

The ACM agreed that the proposed tradename Intuniv is acceptable. ACM noted that in view of Intuniv having already been approved as the trade name by so many international regulators, consistency with these may be preferable to insisting on a different name at this stage.

3. *Absolute approval is dependent on satisfactorily resolving outstanding Module 3 pharmaceutical issues*

The ACM agreed that the pharmaceutical chemistry evaluator has identified multiple issues which remain outstanding and concluded, that approval cannot be recommended from a pharmaceutical chemistry perspective.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Intuniv guanfacine (as hydrochloride) in 1 mg, 2 mg, 3 mg and 4 mg modified release tablet blister packs for oral administration, indicated for:

> *Intuniv is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants). Intuniv must be used as part of a comprehensive ADHD management programme, typically including psychological, educational and social measures*

Specific conditions of registration applying to these goods

The EU-Risk Management Plan (EU-RMP), version 1.5, dated 22 July 2015 (DLP 1 September 2013), with Australian Specific Annex version 1.0, dated 16 February 2017, and any subsequent revisions, as agreed with the TGA will be implemented in Australia as a condition of registration.

Attachment 1. Product Information

The PI for Intuniv approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at < https://www.tga.gov.au/product-information-pi> .

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au