EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2015
EMA/CHMP/534329/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

INTUNIV

International non-proprietary name: GUANFACINE

Procedure No. EMEA/H/C/003759/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

5-HT	5-Hydroxytryptamine
ADHD	Attention deficit/ hyperactivity disorder
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
AUC	Area Under the Concentration-time Curve
BOLD	Blood oxygenation level dependent
cDNA	Complementary deoxyribonucleic acid
C_{max}	Maximum value of the concentration time curve
CNS	Central nervous system
CYP450	Cytochrome P450
DDD	Defined daily dose
DILUTION	Dilution factor
$DOSE_{ai}$	Maximum daily dose consumed per inhabitant
DT50	Degradation half-life (Time for 50% degradation)
EC_{50}	50% effective concentration
ECG	Electrocardiogram
EFD	Embryofetal development
FDA	Food and Drug Administration
Fpen	Market penetration factor
GC	Gas chromatography
GCP	Good Clinical Practice
GI	Gastro-intestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High density polyethylene
HEK-293S	Human Embryonic Kidney 293 cells
HERG	Human Ether-a-go-go-Related Gene
HPLC	High Performance Liquid Chromatography
i.p.	Intraperitoneal
i.v.	Intravenous
IC_{50}	Concentration which results in 50% inhibition
IR	Infra-red spectrometry
IPC	In-process control
Kd	Adsorption coefficient
K_i	Dissociation constant
Koc	Normalised partition coefficient
Kow	Octanol-water partition coefficient
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDPE	Low density polyethylene
LPS	Lipopolysaccharide
MAA	Marketing authorization application
MRHD	Maximum recommended human dose
MRI	Magnetic Resonance Imaging
mRNA	Messenger ribonucleic acid
NADPH	Nicotinamide adenine dinucleotide Phosphate
NMT	Not more than
NOAEL/NOEL	No-observed adverse effect level/No-observed effect level
MS	Mass spectrometry
OECD	Organisation for Economic Co-operation and Development
PBT	Persistence, Bioaccumulation, Toxicity
PCTFE	Polychlorotrifluoroethene
PEC	Predicted Environmental Concentration
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia

pKa	Negative base - 10 logarithm of the acid dissociation constant
PNEC	The Predicted no effect concentrations
PSD	Particle size distribution
PVC	Polyvinyl chloride
RH	Relative Humidity
RTT	Relative retention time
QT_c	Corrected QT Interval
s.c.	Subcutaneous
SH	Spontaneously hypertensive
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half-life
TCL	Thin-layer chromatography
USP	United States Pharmacopoeia
WASTEWinhab	Amount of wastewater per inhabitant per day
WKY	Wistar Kyoto

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shire Pharmaceuticals Ireland Ltd. submitted on 3 March 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for INTUNIV, through the centralised procedure under Article 3 (2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 April 2013. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication: treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 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.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that GUANFACINE was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0265/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0265/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0265/2013.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

INTUNIV has been given a Marketing Authorisation in USA on 2 September 2009 and Canada 5 July 2013.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 3 March 2014.
- The procedure started on 26 March 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2014.
- During the meeting on 10 July 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 24 July 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 January 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 March 2015.
- During the meeting on 12 March 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- The summary report of the GCP inspection carried out at the following sites: Germany (2 investigator sites) and UK (Sponsor and CRO) between 9 of July to 1 of August 2014 in relation to the trial SPD503-316 was issued on 25 November 2014.
- During the CHMP meeting on 26 March 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 10 June 2015.
- During the meeting on 11 June 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 23 June 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 23 July 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to INTUNIV.

2. Scientific discussion

2.1. Introduction

Problem statement

Attention-deficit/hyperactivity disorder is a heterogeneous neurobehavioral disorder characterized by a persistent pattern of developmentally inappropriate inattentiveness, impulsivity, and hyperactivity. The diagnosis of ADHD is made by a healthcare professional who applies either ICD or DSM criteria (American Psychiatric Association 2013). Symptoms of ADHD lasting at least 6 months that cannot be accounted for by another psychiatric disorder must be shown to interfere with age-appropriate functioning in at least 2 settings (e.g., social, academic, or occupational). Based on DSM criteria, there are 3 ADHD subtypes: hyperactive/impulsive, inattentive, and combined subtype. Very high rates of coexisting psychiatric disorders are seen in association with ADHD, and almost two-thirds of children with ADHD have at least 1 additional impairing diagnosis. Depending on the ADHD subtype, sex, and the presence of comorbid disorders, individuals with ADHD may differ considerably, even within a particular age cohort.

Attention-deficit/hyperactivity disorder is one of the most common neurodevelopmental disorders of childhood and, consequently, prevalence rates have been extensively investigated. The worldwide prevalence of ADHD in children is approximately 5%. No significant differences in ADHD prevalence rates between North America, Europe, and other parts of the world were detected in this meta-regression analysis involving 102 studies and 171 756 subjects.

The exact aetiology and pathophysiology of ADHD is unknown; however, it is widely believed that an imbalance in dopaminergic, noradrenergic, and other neurotransmitter systems in the brain contribute to the behavioural sequelae that characterize this disorder. Extensive pre-clinical and clinical research suggests that neurotransmitter deficits, genetics, environment, and perinatal complications may all be contributing factors. It has been hypothesized that the mechanism of action of effective medications in ADHD is to increase levels of neurotransmitters (specifically norepinephrine and/or dopamine, or their precursors) at the synapse either by facilitating release, decreasing reuptake, or by binding and activating the post-synaptic receptor.

Currently, there are both non-pharmacological and pharmacological options (including stimulants and non-stimulants) for the treatment of ADHD. Although limitations exist with the use of either stimulant or non-stimulant medications, such as the potential for side effects, failing to treat ADHD is associated with economic burden and also carries potential risks. These risks may include a higher probability of underachievement in school, low self-esteem, problems with peer interactions, and involvement with crime and substance abuse. Physicians and parents should consider the benefits and risks associated with treating ADHD compared with foregoing treatment.

About the product

Intuniv is a prolonged-release tablet formulation of guanfacine hydrochloride designed for once-a-day oral administration. Guanfacine HCl is a selective alpha2–adrenergic agonist. Its mechanism of action in ADHD is not fully understood; however, non-clinical data suggest it acts by stimulating alpha2A-adrenoreceptors located in the locus coeruleus (midbrain), which projects to the prefrontal cortex and modulates the effects of noradrenergic neurons and noradrenaline on the pyramidal neurons in the prefrontal cortex. These regions are known to play a major role in attention, organization, and planning, along with impulse control. Deficits in these domains may be implicated in the symptoms associated with ADHD. The modulating effect of guanfacine HCl on the noradrenergic tonus of the pyramidal cells in the prefrontal cortex may restore these deficits.

Guanfacine HCl is not a central nervous system stimulant.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as prolonged release tablets containing guanfacine hydrochloride equivalent to 1mg, 2mg, 3mg, and 4mg guanfacine as active substance.

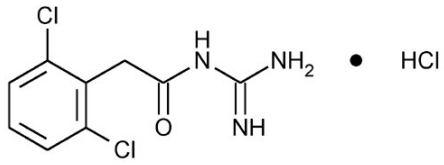
Other ingredients are: hypromellose 2208, methacrylic acid-ethylacrylate copolymer, lactose monohydrate, povidone, crospovidone type A, microcrystalline cellulose, silica colloidal anhydrous, sodium laurisulfate, polysorbate 80, fumaric acid, glycerol dibehenate, indigo carmine aluminium lake (E132) (3 and 4 mg tablets), iron oxide yellow (E172) (3 and 4 mg tablets).

The product is available in PCTFE/PVC/alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of guanfacine hydrochloride is N-(Diaminomethylidene)-2-(2,6-dichlorophenyl)acetamide Hydrochloride and it has the following structure:



The structure of guanfacine hydrochloride was proven by the results from spectroscopy (NMR, MS, UV, and IR) and elemental analysis (EA). The IR and UV spectra were found identical to the Guanfacine HCl reference standard.

The active substance is a white to off white crystalline hygroscopic powder sparingly soluble in water.

The active substance has a non-chiral molecular structure.

References to polymorphism of guanfacine hydrochloride have been found in patent literature. X-ray powder diffraction studies of active substance demonstrate that the same polymorphic form is obtained. Polymorphism is controlled by manufacturing process conditions.

For one of the supplier, the information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterisation and process controls

The active substance is sourced from two suppliers and manufactured by three manufacturing sites. The active substance is synthesized in three main steps using commercially available well defined starting materials with acceptable specifications. A description of the synthesis of one of the starting materials , including a complete discussion on the carry-over of impurities, reagents and residual solvents into the final active substance, was provided. Based on the information provided, the choice of starting material was considered satisfactory. Similar synthetic routes are used by all the manufacturers but different solvents and reagents are used and therefore related substances and impurity profile of the active

substance is slightly different for the two suppliers. However in view of the related substance and impurity levels observed, the active substance qualities from both sources are considered equivalent.

The reprocessing and recovery procedures used by the active substance manufacturers have been adequately described and are considered acceptable.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Potential and actual impurities were well discussed with regards to their origin and characterised. The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

The active substance is packaged in a PE bag which complies with the EC directive 2002/72/EC for one supplier or EC 10/2011 for the other supplier. Primary bag is placed in a polyethylene-aluminium bag. Between the two bags a drying agent (silica bags) is placed. HDPE drums are used as outer container.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), guanidine HCl content (HPLC), residual solvents (GC), loss on drying (USP), residue on ignition (Ph. Eur.), heavy metals (USP), and particle size distribution (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

For one supplier, batch analysis data on four production scale batches of the active substance are provided. For the other supplier, batch analysis data on three production scale batches of the active substance for each manufacturing site are provided. The results are within the specifications and consistent from batch to batch.

Stability

For one active substance supplier, stability data were provided on three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 9 months under long term conditions at 25 ºC / 60% RH and 30°C/65%, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: appearance, identification, LOD, purity by HPLC, guanidine HCl content and assay. The analytical methods used were the same as for release and were stability indicating.

All results were within specification limits. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

For the other active substance supplier, stability data on sixteen production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 60 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, water content, purity by HPLC, guanfacine HCl content (TLC) and assay. The analytical methods used were the same as for release and were stability indicating.

All results were within specification limits. The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Photostability studies have been performed as part of analytical method validation studies. Results indicate that the active substance is not light sensitive.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of the pharmaceutical development was to develop a prolonged-release tablet formulation of guanfacine hydrochloride designed for once-a-day oral administration.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2.1.1 above and in section 6.1 of the SmPC.

Aspects related to the paediatric use of the product such as safety of excipients in children, patient acceptability, risk of chewing, compatibility with food and/or drinks have been satisfactorily discussed.

The objective of the early formulation development studies was to design matrix tablet formulations by the selection of functional excipients that would optimize the active substance release from the dosage form over the pH range of the gastrointestinal tract. Guanfacine, a weakly basic active substance, has pH dependent solubility and exhibits higher solubility at acidic pH conditions than at basic pH conditions. The range of release profiles was achieved through the selection of the nature and the level of the functional excipients to be used in the formulation

The manufacturing process development studies for the matrix tablet formulations focused on direct compression. Thus, in addition to the prolonged-release functional excipients, the formulations studied included various tablet diluents designed for direct compression applications. The excipient grade selections were based on the compatibility of the particle size distributions reported for the two excipients used as diluents.

Three 1 mg tablet formulations were evaluated in a Phase I study designed to compare the bioavailability and pharmacokinetic profile of the prolonged-release formulations to that of a 1mg immediate-release commercial product (TENEX). The conclusions of this study were that the three experimental formulations had prolonged-release characteristics as compared to the immediate-release reference formulation. The formulation with the medium release profile had the most favourable prolonged-release characteristics based on the rate and extent of absorption and thus was selected as the basis for further development of the finished product.

Along with the original 1mg dose, 2mg, 3mg and 4mg doses were developed. This work entailed the formulation blend development and the selection of tablet size and tablet shape for each of the dose strengths. The desired manufacturing scheme was to have two direct compression powder blends, with minor tablet colour dye modifications, as needed, for dose differentiation. One common blend was developed for the 1 mg and 2 mg doses and a second for the 3 mg and 4 mg doses.

In order to accommodate reasonable tablet sizes for the various doses, active substance concentration was increased for all strengths power blend.

Representative batches of the 1mg, 2mg, 3mg and 4mg dose tablets were evaluated for dissolution in a comparative manner to batch selected during Phase I study. The results indicated that the reformulated powder blends produced tablets with similar dissolution profiles to the Phase I clinical batch, based on the f2 similarity metric.

Except for Phase I Study, the formulation used during clinical studies is the same as that intended for marketing.

The dissolution and bioequivalence studies results provided fully supports the transfers of the manufacturing process from the different manufacturing sites and the change in manufacturing process. However, it was not considered acceptable that no dissolution studies at all have been performed at pH 1.2 and at pH 4.5. The CHMP recommended to perform dissolution studies at pH 1.2 (by applying a sample neutralisation procedure) and at pH 4.5 for representative drug product batches, i.e., for one batch per strength (1, 2, 3, and 4mg) manufactured at the proposed manufacturing site utilizing proposed process. Dissolution results for the aforementioned studies should be provided within 6 months after Community Decision.

An active substance overage is used to compensate for manufacturing losses and was considered justified.

Description of the development of the proposed dissolution method is provided. The choices made for establishing initial dissolution method have been described including a rationale for the apparatus, dissolution media, use and choice of surface active agents, rotation speeds and sink conditions. The discriminatory power of the dissolution method is considered to be demonstrated.

The primary packaging is a blister strip comprised of 2 layers, a clear thermoformable rigid film which is laminated with PCTFE and a PVC backing to which a push-through aluminium foil is adhered. The blisters are contained in cardboard cartons. The primary packaging materials comply with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: excipient screening, blending and sieving/milling of the active ingredient with excipients followed by direct compression and packaging. The product is manufactured using conventional manufacturing techniques but the manufacturing process is considered a non-standard process due to the low amount of active substance per unit and the prolonged release characteristics. The blending step is considered critical for uniformity of dosage unit and for modified release characteristics as it is a matrix releasing product. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The process validation for the guanfacine HCl prolonged-release tablets was performed on production scale batches utilizing a matrix approach that was considered acceptable. All batches met the set acceptance criteria or specifications. Holding time used for bulk tablet was also validated. Based on the data provided the process is considered validated.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC-UV), content uniformity (Ph. Eur.), assay (HPLC), impurities (HPLC), dissolution (USP dissolution apparatus 2 and HPLC-UV), microbiological quality (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Impurities present at higher level than the qualification threshold according to ICH Q3B were qualified by toxicological and clinical studies and appropriate specifications have been set.

Given the manufacturing process (direct compression), a limit for polymorphic form in the finished product is not considered necessary.

The absence of hardness, friability and water content testing in the finished product specifications was considered justified.

Batch analysis results are provided for two pilot scale batches and one production scale batch per strenght confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 2 pilot scale and 2 production scale batches of finished product for each strength stored under long term conditions for up to 48 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, related substances, dissolution and microbiological quality. The analytical procedures used are stability indicating.

No significant difference was observed between the stability results of the full-scale batches and the stability results of the pilot-scale batches. All stability results comply with shelf-life specifications.

As only two production scale batches of each strength are included in the stability studies, the CHMP recommended performing finished product stability studies on an additional production scale batch of each strength at long term and accelerated conditions.

In addition, forty guanfacine HCl prolonged-release tablets of each strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results showed that prolonged-release tablets are not light sensitive.

Based on available stability data, a shelf-life of 48 months without any storage conditions was granted and stated in the SmPC.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The selection of functional excipients that would optimize the active substance release from the dosage form over the pH range of the gastrointestinal tract was described. Aspects related to the pediatric use of the product such as safety of excipients in children, patient acceptability, risk of chewing, compatibility with food and/or drinks have been satisfactorily discussed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics such as dissolution, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to perform dissolution studies at pH 1.2 (by applying a sample neutralisation procedure) and at pH 4.5 for representative finished product batches, i.e., for one batch per strength (1, 2, 3, and 4mg) manufactured at the proposed manufacturing site utilizing the bin blending process at both 55kg and 300kg scale for guanfacine hydrochloride prolonged release tablets. The dissolution results for the aforementioned studies should be provided within 6 months after Community Decision

- to perform finished product stability studies on an additional production scale batch of each strength at long term and accelerated conditions

2.3. Non-clinical aspects

2.3.1. Pharmacology

Guanfacine is a moderately potent ligand for the human form of the α_{2A}-adrenoceptor with 15 to 20 fold binding selectivity for human α_{2A}-adrenoceptors over the α_{2B}- and α_{2C}-subtypes.

Various behavioural models in rats and primates suggest that guanfacine may improve cognitive and behavioural performance by an action at postsynaptic α_{2A}-adrenoceptors in the frontal cortex. These findings include: Dose-dependent (0.3 or 0.6 mg/kg, i.p.) reduction of impulsiveness and hyperactivity of male spontaneously hypertensive (SH) rats and improved sustained attention in SH rats with its maximum effect at 0.3mg/kg, i.p.; Improvement of the performance of male, wild-type control mice in the delayed alternation task (1 mg/kg, i.p.); Dose dependent improvement of spatial working memory in young adult female monkeys (0.1 – 0.7mg/kg, i.m.); and improvement of visuomotor associative learning in monkeys (0.001 or 0.1mg/kg, i.m.).

The cognitive effects of guanfacine were abolished by co administration of the selective α_2-adrenoceptor antagonist idazoxan (0.1mg/kg, i.m.).

Taken together these data support the development of guanfacine for the treatment of ADHD in children. Yet, it is also noted that the effects may be age-dependent. Improvement in memory and retention (0.001mg/kg, i.p.) have been demonstrated in normal, young, Wistar rats using the Morris water maze, but the same model showed no effects in adult rats. Also, improvement of spatial working memory was dose-dependent in young adult female monkeys, but in aged monkeys an effect was observed at low and high doses, but not at intermediate doses.

Guanfacine is extensively metabolised, both in humans and in animals (see pharmacokinetics section). No information is provided on the primary pharmacological activity of relevant human metabolites. Additional information on the main human metabolite 3-hydroxyguanfacine sulfate should be provided by

the Applicant. If drug interactions leading to increased levels of the intermediate metabolite 3-hydroxyguanfacine are suspected additional information on this metabolite is warranted as well.

The affinity of guanfacine (10^{-7}, 10^{-6}, 10^{-5} M) for a wide range of receptors, ion channels, ancillary binding sites, transporters and enzymes has been determined *in vitro* using radioligand binding techniques. For those receptors/sites where guanfacine displaced ≥ 50% of the specific binding, a more comprehensive radioligand displacement analysis was performed. The results suggest that for most of the investigated receptors, ion channels and enzymes no relevant pharmacological action is expected, but agonist activity at the 5-HT_{2B} receptor could be clinically relevant. Consequently, valvulopathy was included as a potential risk in the RMP.

The published literature shows that relatively low doses of guanfacine are analgesic, anticonvulsant, antinociceptive, possibly anxiolytic and sedative. The sedative properties are mediated via α_{2A}-adrenoceptor activation at dose levels similar to those where the primary pharmacological effects are induced.

Experimental data demonstrate a clear hypotensive action of guanfacine, which is manifested as a lowering of systolic and diastolic blood pressure with a reduction in peripheral vascular resistance that may or may not be accompanied by a reduction in heart rate. Hypotension and potentially bradycardia are, therefore, predicted side effects for the use of guanfacine in the treatment of ADHD.

In an *in vitro* hERG channel study, no relevant inhibition of I_{Kr} could be shown up to 1 µg/mL. In telemetered dogs no significant effects on arterial blood pressure, QRS duration, QT, QTcF, or QTcQ intervals were observed, but there was a pronounced bradycardic effect after 0.5 or 1.5 mg/kg. The lack of ECG effects contrast with those reported for the 52 week repeated dose toxicology study as described in the FDA Summary Basis of Approval (SBA) for Tenex. In this study increase of QTc was reported. The main human metabolite 3-hydroxyguanfacine sulfate is not expected to affect cardiac conductance, but if drug interactions leading to increased levels of the intermediate metabolite 3-hydroxyguanfacine are suspected additional information on this metabolite is warranted.

In various animal models, contradictory effects of guanfacine on respiration were reported.
The Applicant concludes that the literature evidence suggests that guanfacine is unlikely to have any adverse effect on respiration at therapeutic dose levels. However pharmacokinetic data are not available for the cited studies and the doses were not really high, thus, also in view of the conflicting data, it is difficult to conclude on the relevance for humans.

Radioligand binding studies and experimental studies *in vivo* suggest that guanfacine treatment could increase urine and sodium output, by a centrally-mediated mechanism.

Direct inhibitory actions on gastric emptying and intestinal motility are relevant at the therapeutic doses and possibly related gastrointestinal adverse events (e.g. abdominal discomfort, diarrhoea, constipation) are described in the current prescribing information for guanfacine products.

In vitro studies in mouse macrophages suggest that guanfacine potentially may augment cell-mediated immune response through increased IL-12 secretion. In contrast, in various *in vivo* models in rats and rabbits anti-inflammatory properties were shown.

Studies in rats and mice showed a decrease in basal metabolic rate reductions in food intake, weight gain, and food conversion efficiency associated with hypothermia. In mice severe glucosuria was shown, suggesting it may be one of the mechanisms that is responsible for the weight loss observed in mice after guanfacine administration.

Various effect on the adrenal system were shown, including an inhibititory effect on carbachol-stimulated synthesis of [^{14}C]catecholamines, possibly by suppression of tyrosine hydroxylase activity. Also in SH rats a ~20% decrease of pretreatment values of catecholamine secretion rates and a ~60% reduction of adrenal plasma flow rate was shown. Since α_{2A}-adrenoceptors are present in the human adrenal gland along with the α_{2B}- and α_{2C}-adrenoceptors, these findings may be clinically relevant to guanfacine's hypotensive properties.

Results from a pharmacodynamic interaction study in SH rats indicate that combination of sub-effective doses of guanfacine and d-amphetamine do not improve ADHD-related behaviours. It is not clear whether combination of effective doses would lead to further improvements. It also unknown whether these results can be extrapolated to combination of guanfacine with other psychostimulants, for instance the more widely used methylphenidate. Nevertheless, these data are of minimal relevance for this MAA, since currently only guanfacine monotherapy is applied for.

2.3.2. Pharmacokinetics

Analytical methods

The methods of analysis of guanfacine in rat, mouse and dog plasma in applicant-sponsored studies were based upon liquid-liquid extraction followed by LC-MS/MS c.q. UPLC/MS/MS. Full validation reports were provided.

Absorption and kinetics after a single dose

In male rats, dogs and monkeys, absorption of total drug related material, as determined by liquid scintillation counting after oral administration of a single [^{14}C]-radiolabelled dose of 1 mg/kg guanfacine was fast, with plasma T_{max} of 0.5 to 2 h. In rats, a second plasma peak at 8 h suggested enterohepatic circulation. Based on recovery of radiolabel in urine, absorption in the rat was at least 37%, in the dog 81% and in the monkey 61%. Biotransformation was fast: in all three species at T_{max} about 4-5% consisted of unchanged parent compound.

In male and female dogs, after a single oral dose of 0.3 - 3 mg (non-labelled) guanfacine/kg, absorption of unchanged parent compound was fast with T_{max} of 1-2 h, except for the high dose females (10 h). No evidence of sex related differences was observed, AUC values increased approximately dose proportionally, the mean elimination half-life was about 1 h to 3.5 hr.

Limited absolute bioavailability data were reported for guanfacine in animal and human. Based on the amount recovered in the urine, at least 78%, 77%, and 37% of the dose was absorbed in human, dog, and rat, respectively.

Repeated dose toxicokinetics in mice, rats and dogs

In mice, at achieved dietary doses for 14 days of 0.4, 1.2 and 8.4 mg/kg/day in males and 0.6, 1.2 and 18.8 mg/kg in females, systemic exposure at the lowest doses increased approximately dose related. At the high dose level, less than proportional increase of systemic exposure suggested saturation of absorption. Due to differences in achieved doses, no conclusions regarding time-related changes in exposure could be drawn. No gender comparison was possible, since the females consumed higher doses.

In rats, at achieved dietary doses for 14 days of 0.4 to 4 mg/kg/day, systemic exposure increased with increasing dose levels. At the lowest doses, dose proportionality and difference in exposure between day 1 and 14 could not be assessed due to lack of quantifiable plasma concentrations. At the highest dose, systemic exposure to guanfacine was about 2-3 fold higher on day 14 compared to day 1 of dietary administration and systemic exposure to guanfacine was higher in females compared to males. A second repeated dose dietary study in male rats also suggested increase of exposure (factor 1.5) between days 4 and 94. Comparison of systemic exposure in rats treated by dietary and gavage administration suggests that dietary administration results in much lower bioavailability.

Rat gavage toxicokinetic studies showed no consistent gender differences at low doses, but at higher doses, female rats had higher exposure than male rats. In these studies, in general, exposure in rats to guanfacine increased more than dose proportional.

In rat juvenile toxicity studies with (gavage) administration periods of postnatal day 7 to 59 or 98, exposure decreased from day 13 to day 53 or 96. Exposure during the first week of administration was not studied. Considering the young age during the first treatment week and the decreasing exposure between day 13 and the end of each study, it could be expected that exposure during this first week may have been higher than on day 13.

In dogs, systemic exposure to guanfacine after single and 14 days repeated oral (capsule) dosing at doses of 0.3, 1 and 3 mg/kg/day, increased approximately dose proportionately. A possible trend towards an increase in systemic exposure on Day 14 compared to the first dose, was not consistently observed across all dose levels and between sexes. There were no consistent sex related differences.

Distribution

According to literature data, plasma protein binding data in the rat and man is similar: 20-30%. However, the value for humans may be incorrect since in the same report also a protein binding value of 64% is mentioned for man. The reliability of the reported values for rats cannot be assessed either. The applicant provided satisfactory data concerning plasma protein binding in the relevant laboratory species during the procedure.

The whole blood to plasma ratio of radioactivity after administration of [^{14}C]-guanfacine in rats, monkeys and dogs is about 0.60, indicating that the radioactivity did not distribute significantly to red blood cells. This is based on estimates of radioactivity, consisting only for a small part of unchanged parent compound. Measurements of unchanged guanfacine in red blood cells are not available for laboratory animals.

A published study describing the distribution of [^{14}C]-guanfacine after single and repeated oral administration of 2 mg/kg/day in male albino rats showed wide distribution of radioactive material in the tissues, with at the first sampling point (2 h) the highest levels in kidney and liver, followed by lung. Due to timing of sampling points, peak levels may have been missed. This may explain why a lag-time of distribution to brain tissue (reported in literature, of interest in view of its central site of action) was not observed. The range of sampled tissues was limited. Concentrations in intestinal tract, bone marrow and thyroid, pigmented tissues (eye) and female reproduction organs of non-pregnant females, were not studied. According to published information, high levels in intestinal tissues after IV administration in rats indicate biliary excretion.

Repeated oral dosing for 1 or 2 weeks only increased the concentrations slightly. In view of the fast biotransformation of guanfacine in the rat most detected radioactivity may have consisted of metabolites. However, published information indicates that the parent drug may be the major constituent of the radioactivity in the rat brain. Also in the rat foetus most radioactivity consisted of unchanged parent compound. In adult rat liver the relative concentration of unchanged parent compound compared to metabolites was higher than in plasma. This points to a relatively high uptake of unchanged parent compound into tissues from the circulation and/or slower degradation of material after absorption into tissues.

A published study in pregnant rats (GD17, single dose of 2 mg/kg[^{14}C]-guanfacine) supplemented the overall distribution study in male rats with data in brain, liver, blood and placenta of pregnant female rats, in foetal brain and liver and in amniotic fluid. The concentration in amniotic fluid lagged behind the peak in maternal blood. Although overall exposure of the foetus was much lower than that of the dam, and disappearance of radioactivity from all tissues mirrored that in maternal blood, the concentration in foetal brain was relatively high and only little lower (early time points) or even higher (late time points) than that in the maternal brain. According to other published information, after a single oral dose of 5 mg/kg [^{14}C]-guanfacine in pregnant rats (GD18), high levels of radioactivity occurred in foetal lungs and intestine, but radioactivity was not observed in foetal blood or amniotic fluid. During the procedure the applicant clarified the differences in results between the published studies in a satisfactory manner.

Metabolism

In vitro

Rabbit liver microsomes, but not pig or human liver microsomes, catalysed the formation of N-hydroxyguanfacine, only in presence of NADPH. Microsomes from all three species catalysed the reverse N-reduction of N-hydroxyguanfacine to guanfacine, in the presence of NADPH. No *in vitro* data on other metabolites in rabbits were available. Not any *in vitro* data for other laboratory species used in the major toxicity studies were provided.

A series of *in vitro* metabolism and pharmacokinetic interaction studies in human *in vitro* test systems were provided. For summary and conclusions from these studies see the Clinical AR.

In vivo

In vivo metabolism data in rat, dog and monkey after a single dose, showed that in all three species, [^{14}C]-guanfacine was degraded quickly to a large number of metabolites.

At T_{max} in the rat, unchanged parent drug in plasma represented less than 5% of the total radioactivity, a sulfate conjugate of a hydroxy-guanfacine represented 34 % of the radioactivity, and a sulfate conjugate of a dihydroxy-guanfacine represented 13 % of the radioactivity. Ten other radioactive components were identified in plasma at this time point. In a published rat study, two glucuronides and a sulfate accounted for most of the radioactivity at a slightly later time point, and smaller amounts of mercapturates and of OH-guanfacine were found. In addition to oxidation and sulfation, epoxidation, glucuronidation, cysteine conjugation, acetylation, hydration, dealkylation, methylation may play a role in the rat.

In the dog, similar biotransformation reactions as in the rat are plausible, but in addition also evidence of dehydrogenation was noted. Unchanged parent drug accounted approximately 7 to 8% of the radioactivity in the 1 and 4 hour pooled plasma samples, two major metabolites were guanfacine dihydro-diol (22 to 36% of the radioactivity) and a sulfate conjugate of a hydroxyguanfacine (24 to 33% of the radioactivity).

In the monkey, unchanged guanfacine represented 7.5% of the total radioactivity AUC, major metabolites were hydroxyguanfacine sulfate (66% of the radioactivity AUC), guanfacine-2H (8.7% of the AUC). Fifteen other radioactive components with lower concentrations were detected in plasma.

According to published information, radioactivity in tissues (brain, liver, foetus) consists for a larger part of unchanged parent compound than radioactivity in plasma.

The major circulating metabolite in man is sulfate conjugate of 3-hydroxyguanfacine. This metabolite is also present at sufficient levels in the laboratory animals (rat, dog) used for safety studies.

There is no information whether any of the above mentioned metabolites may be pharmacodynamically active.

Excretion

Excretion of radiolabelled material after a single oral dose of 1 mg [^{14}C]-guanfacine/kg was investigated in two male rats, dogs and monkeys. In a period of 72 h rats excreted most (56 %) of the radioactive dose in faeces, and less (37 %) in urine. In 72 h, dogs and monkeys excreted most of the dose (77 % and 61% respectively) in urine and only small amounts (3 and 6% respectively) in faeces. Most of the dose was already excreted in the first 24 hrs after administration. In rats and monkeys, high recovery indicated almost complete excretion over the 72 hr study period. A lower recovery (80 %) in dogs suggested that excretion was not complete during this period. Excretion in bile was not investigated. In the rat, plasma profiles suggested enterohepatic circulation. In monkeys and dogs only little material was excreted in faeces and no plasma peaks suggesting enterohepatic circulation were observed.

According to a publication, low amounts are excreted in rat milk.

Metabolites in excreta

In rat and monkey urine, parent compound accounted for only a very small part of the total radioactive dose. About 32% of the total radioactive dose was excreted in dog urine as the unchanged parent compound. In rat faeces, unchanged parent compound accounted for about 6% of the dose and all other components were present in smaller quantities. In dog faeces, all components including parent compound accounted for < 1% of the dose. In monkey faeces, no parent compound was detected and the component accounting for the highest part of the dose, about 3%, was probably 3-hydroxyguanfacine.

Overall, metabolites in urine and faeces of rats, dogs and monkeys were consistent with the metabolic pathways suggested by the metabolites found in plasma. Most of the excreted metabolites were present in minor quantities, with the exception of about 32% of the dose excreted as unchanged parent compound in dog urine. It can be concluded that metabolism in dogs is less extensive than in rats and monkeys.

Pharmacokinetic drug interactions

In a juvenile rat study, in which guanfacine was administered from day 7 to 59 in combination with methylphenidate, exposure of both guanfacine and methylphenidate on day 13 and day 53 was higher than with each compound alone.

2.3.3. Toxicology

Single dose toxicity

Two acute dosing studies are submitted by the applicant, showing that high doses of guanfacine elicits glucosuria and leads to poor condition of the animals in general, presumably due to exaggerated pharmacology. Further, effects on eye are seen with high doses in rat and mice.

Repeat dose toxicity

Repeated dose studies with guanfacine in mouse, rat and dog from different sources (literature, Tenex SBA (1986) and studies directed by applicant) have been submitted by the applicant.

Treatment of animals with guanfacine clearly affected food consumption and body weight. Decreases in BW are found in mouse and rat at exposure levels that are below human exposure levels. However, in dog the BW decrease was only seen at exposure levels 2-3 times above human exposure levels. In the clinic, rather an increase in BMI is observed. Increase in blood glucose levels was rather an acute finding. In the long term studies a decrease in glucose levels was seen in animals. This decrease in glucose was also observed in some small clinical studies with an alpha 2 agonist in diabetic patients, which led to the effect that some patients even could decrease the dose of antidiabetic drugs and insulin. It seems that an acute response to alpha 2A adrenergic receptor agonists appears to ameliorate over time. Thereby, the pancreatic findings in animals appear to be relatively diverse and not exclusively observed in treated animals. In addition, findings are often not observed in recovery groups. No deleterious changes were seen in the endocrine part of the pancreas.

Guanfacine administration to animals revealed toxicological effects in organs and functional systems, which are summarized and discussed below:

Heart: In dogs (52 weeks), treatment of guanfacine resulted in increase of incidence and intensity notched T-wave (0.3 mg/kg/day) and prolongation QT-interval (1.0 mg/kg/day). The dose of 0,3 mg/kg/day corresponds to exposure levels of 18,57(m) and 38,21 ng.hr/mL in (f) and C_{max} values of 5.56 (m) and 9.69 (f) ng/mL below clinical exposure and C_{max}. Though the applicant raises the argument that it may not have been corrected for heart rate. An effect on heart rate, blood pressure and QT-interval is also observed in clinical studies. Furthermore, the Applicant states that Ki for 5-HT_{2B} is 100 fold higher than for the adrenergic receptor. Yet, considering the actual plasma exposure and the EC50 values measured for guanfacine at the 5-HT_{2B} receptor the difference is rather small. A potential clinical relevant

activity of guanfacine at this receptor cannot be excluded (see for details in secondary pharmacology section). Therefore, heart functioning, and more specific prolongation of QT interval, will be monitored in patients treated with guanfacine and included in the RMP.

Immune system & coagulation parameters: In general, hematocrit, hemoglobulin and red blood cells were decreased due to treatment. Atrophic and anemic spleen (1,0 mg/kg/day, 52 weeks) and mall and contracted thymus & Lymph Nodes (3.0mg/kg, 90 days) were seen in dogs, below clinical exposure levels. Male mice (dosed 10 mg/kg/day, 78 weeks) had lymphopenia (low WBC levels) and levels of several types of white blood cells were affected in rat, but not always in both sexes. In clinical studies a few participants showed a marked decrease in white blood cells. This could possibly reflect idiosyncratic immune mediated effects which should be monitored post-marketing and reported in the PSURs.

Liver: Liver biomarkers in blood, like bilirubin and ALT are increased in the male dogs dosed 3.0 mg/kg/day guanfacine for 52 weeks slightly higher exposure then clinical. Microscopic effects seen in dogs start already at a dose of 1.0 mg/kg/day (90 days) in dog (moderate fatty change), corresponding to exposure levels of 63,26 (m) and 82,15 ng.hr/mL (f) in dog, below clinical exposure levels. Increases in bilirubin and ALT are seen at a higher dose, at exposure levels slightly higher than human exposure levels.

Intestines affected in rat: Intestine shows diffuse dilatation & wall thickening((5 mg/kg/day, 102 weeks, below clinical exposure levels.) and submucosal oedema and inflammation at higher doses in short term studies. An increase in GI tract minimal or moderate adverse events associated with guanfacine has been observed in the clinical programme.

Kidney: Changes in kidney biomarkers in rat like - increased creatinine & blood urea nitrogen levels (also in dog) and decreased total protein & albumin levels 1 mg/kg/day) in rat were seen in short term studies, below clinical exposure levels. In the long-term (dog and rat) decreased levels of cations were found in urine. Microscopically symptoms started at relative high doses. Relevance in human in not so likely since these effects have not been reported in clinical study.

Eye: An increase in corneal opacity is seen in mice (10 mg/kg/day for 78 weeks) and corneal clouding in rat at low dose (0.5 mg/kg/day for 102 weeks or 10 mg/kg/day for 26 weeks). Stromal inflammation in eye and infiltration of inflammatory cells in the cornea were seen in rat at higher doses. No coneal clouding was observed in humans. Blurred vision was occasionally noted in patients, but this seems unrelated to the corneal clouding seen in animals.

Spermatogenesis: Several dogs treated for 90 days with 10 mg/kg/day guanfacine showed affected spermatogenesis: vacuolar changes of spermatogenic cells (1m) & reduction of spermatogenesis in testes (1m) and spermatophagic granuloma epididymis (1m).Male fertility in rat was effected at the lowest dose of 8 mg/kg/day (see reproductive toxicity studies). Therefore adverse effects on male fertility were included in the SPC.

Genotoxicity

In vitro genotoxicity: No mutagenic potential has been shown in two *in vitro* genotoxicity tests (Ames test and chromosomal aberration test) with guanfacine, in absence or in presence of rat liver metabolic activation system S-9. However, it is not clear whether all human relevant metabolites were formed using rat-S9. Therefore the applicant is requested to discuss to which extent the provided genotoxicity tests are of relevance, paying special attention to formation of metabolites in humans and by S-9 mix.

In the *in vitro* chromosomal aberration test, sporadic increases in the frequency of numerical aberrations were observed, primarily in the presence of S-9, following treatment with pure and impure guanfacine hydrochloride. The increases were small and were not well reproduced between experiments. As the

assay is not specifically designed to detect numerical chromosome aberrations, these findings were not considered biologically relevant.

In vivo genotoxicity tests performed for registration of TENEX and assessed by the FDA did not indicate mutagenic potential of guanfacine.

Carcinogenicity

Only descriptions of previous studies with guanfacine in the FDA SBA were provided by the applicant in the first place. The applicant stated that Clinical and post-marketing data analysis for guanfacine, which has been available to the public in various formulations for 24 years with an exposure of approximately 3 million person years, do not provide any indication of a carcinogenic risk.

In addition the applicant provided an assessment document from the FDA for registration of TENEX, which contained the assessments of two carcinogenicity studies. The carcinogenic potential of guanfacine was evaluated in a 78 weeks study in mice and a 102 weeks study in rat. A significant increased incidence of adenomas of the pancreatic islet in the high dose treated rats was reported.

Further to the review of the submitted data, the CHMP considered that insufficient information was available to assess the carcinogenic potential of guanfacine. The Applicant was requested to review the available data relevant for assessing the risk for carcinogenic potential of guanfacine, especially with respect to pancreatic islet adenoma's, since these were present with an increased incidence in high dose males in a carcinogenicity study described in the FDA SBA for Tenex. It appeared that the increased incidence noted in this study can probably be explained by the increased survival leading to increased exposure times. The lack of any effect in females or in mice and the lack of any carcinogenic potential of other α2 AR agonists (clonidine, lofaxedine) gave further reassurance that the signal in the rat carcinogenicity study is unlikely to be of relevance for humans. The lack of any guanfacine-related tumorigenicity was also supported by post-marketing experience with Intuniv in the US, although limited to 5 years. , in these patients is in support of this conclusion. Therefore this issue was considered as resolved by the CHMP and Routine monitoring of tumorigenicity after MA were considered sufficient as post-marketing surveillance

During the procedure the Applicant reviewed the available data relevant for assessing the risk for carcinogenic potential of guanfacine, especially with respect to pancreatic islet adenoma's, since these were present with an increased incidence in high dose males in a carcinogenicity study described in the FDA SBA for Tenex. It appears that the increased incidence noted in this study can probably be explained by the increased survival leading to increased exposure times. The lack of any effect in females or in mice and the lack of any carcinogenic potential of other α2 AR agonists (clonidine, lofaxedine) gives further reassurance that the signal in the rat carcinogenicity study is unlikely to be of relevance for humans. Although the post-marketing experience with Intuniv in the US is still limited to 5 years, a lack of any guanfacine-related tumorigenicity in these patients is in support of this conclusion. Routine monitoring of tumorigenicity after MA was considered sufficient as post-marketing surveillance.

Reproduction Toxicity

In reprotoxicity studies guanfacine was administered via oral gavage. In bridging toxicokinetic studies animals were treated with guanfacine via dietary administration. Therefore, no proper toxicokinetic data is available for the fertility, EFD and PPND studies presented by the applicant in the dossier. Consequently, extrapolation to humans and predicting the clinical relevance is difficult. However, considering the whole package of available toxicokinetic data, it is plausible that exposure at maternal / foetotoxic doses in the animal studies was within the therapeutic range in humans or at most only slightly

above. So it is unlikely that, if toxicokinetic data would have been available, exposure margins significantly higher than a factor 1 or 2 would have been found.

Fertility studies with Guanfacine

No effect on fertility was observed in male and female mice at the highest dose tested 2.0 mg/kg/day (NOAEL) estimated around clinical exposure levels. Fertility in female rat (Tenex SBA, 1986) was unaffected when tested up to 16 mg/kg/day, but male fertility was affected at the lowest dose tested (8 mg/kg/day). These findings were included in the SPC.

Embryonic and Foetal development studies with Guanfacine

Studies evaluating embryonic and foetal development in mice and rabbit (literature) and in rat and rabbit (Tenex SBA, 1986) have been submitted by the applicant. Due to decreased BW in dams and malformations / teratogenicity (specific for mouse strain) in offspring the NOAEL for F0 and F1 is 0.5 mg/kg/day in mice. Due to BW decrease in mothers and a case of oligodactily in pups, NOAEL for F0 and F1 was the lowest tested dose of 0.5 mg/kg/day (literature). In the TENEX study the NOAEL was the lowest tested dose of 1.0 mg/kg/day. Comparison based on mg/m^2 suggests that effects are seen at doses similar to human doses. Due to decreased BW in dams and foetotoxicity in offspring the NOAEL for F0 and F1 is 1.0 and 3.0 mg/kg/day respectively (TENEX SBA, 1986).

Overall, teratogenicity has been observed in mice after treatment with clinically relevant doses of guanfacine. In rats and rabbits no teratogenic effects were observed. Foetal toxicity observed was in presence of maternal toxicity. The evaluation of adversity of the effects is hampered due to presence of maternal toxicity already at low doses. Therefore, adverse effects in humans cannot be ruled out. Currently there is no or limited data regarding use of guanfacine during pregnancy published. In animals, potential strain specific teratogenicity is observed in mice and foetotoxicity in rat and rabbit. All effects seen in EFD studies were in the absence of proper toxicokinetic data. Preclinical findings and the lack of information on use of guanfacine in human during pregnancy lead to the conclusion that Guanfacine should not be recommended during pregnancy. This was reflected in the SmPC.

Peri and Post natal development studies with Guanfacine

Studies evaluating effect of guanfacine treatment upon pre and post-natal development in mice (literature) and rat (Tenex SBA 1986) were submitted. In both studies, the NOAEL was the lowest dose tested, thus 0.5 mg/kg/day for the literature study and 2.0 mg/kg/day for the TENEX study. Dams treated with the high dose had a lack of milk, which was regarded as a sympathomimetic action of the drug in the dams, which was reflected in the SmPC.

Juvenile studies with guanfacine

A 7 weeks and a 90 days study with guanfacine only and a combination study with guanfacine and methylphenidate in juvenile rat were submitted. Justifications for the choice of the test species found in the study reports only refer to general statements such as that the rat is generally accepted by regulatory authorities, that the laboratory has experience with this species and that guanfacine has been studied in the rat before. However, in view of differences in pharmacokinetics between laboratory species and humans, it can be questioned if the rat has been the optimal choice. In the rat guanfacine is rapidly metabolised and most of the parent compound has disappeared from circulation within half an hour. The slower clearance in humans and the prolonged release formulation proposed for Intuniv would lead to a significantly different exposure profile of guanfacine in humans. Thus, a drawback of the use of rat as test species is the rapid clearance leading to relatively low plasma levels during a large part of the day. Nevertheless Cmax levels in the high dose animals exceeded human Cmax levels.

Guanfacine administration from d7-d59 showed BW decrease and related symptoms as delay in sexual maturation and increased activity (ambulatory activity, increased max. times on rotarod). Other changes were also observed in repeated dose toxicity studies in adult animals.

Guanfacine administration from d7-d97 resulted in resistance to dosing, agitation, tenseness and vocalisation in females animals at the end of the study. In addition, starting from day 80, animals showed abnormal behaviour 1,5-3 hr post-dose such as intermittently standing still, inactivity, unsteady gait, fixed gaze, etc.. From day 92 on, these symptoms were noted for even longer periods post dose, up to 5 hr. During recovery, no treatment-related effects were observed. Above described symptoms are contradictory with the observed increased ambulatory activity and increased times on the rotarod, observed on d44-52 in the shorter juvenile toxicity study (d7-d59). These findings might be related to the neuropharmacological properties of guanfacine, which may potentially affect neurodevelopmental processes in early phases of brain development leading to changes in neuropharmacological response and behavioural outcome at later stages in life. This was further discussed by the Applicant during the procedure.

The design of the juvenile study does not fully reflect the developmental phase of the patients to be treated. Whereas exposure in the rat juvenile study encompasses the period of highest monaminergic transmitter receptor expression (including alpha 2 A receptors), the intended age group in humans does not. Therefore, in theory, in the rat study neurodevelopmental processes may have been affected, that possibly would not be affected in humans when exposure starts at the age of 6. Furthermore, behavioural signs may also occur when rats are exposed at later stages without exposure at these early phases in life. This suggests that the observations are mostly direct pharmacological effects. The finding in the juvenile toxicity study that the incidence and intensity of the behavioral signs increased during the late stages of the study may reflect a particularly sensitive period in these animals. The nature of the symptoms are also remniscent of overdose symptoms in pediatric patients. This too gives the impression that the observations are rather exaggerated pharmacological symptoms.

Although definitive answers on neurodevelopmental perturbations cannot be derived from the juvenile study, the behavioural symptoms that were observed were sufficiently discussed.

The NOAEL for juvenile toxicity, based on BW decrease in the 90 days study, is 0.3 mg/kg/day corresponding to exposure of 9.81 (m) and 11.1 (f) ng.hr/mL at day 13 and 4.70 (m) and 5.55 ng.hr/mL (f) at day 96 of age), which is below clinical exposures. Higher dosages could not be achieved however, due to dose limiting reductions in body weight seen in the DRF study. Body weight decrease, however, is not reflecting clinically outcome in humans, as the opposite is observed in children, which show an increase in body weight gain.

Combining guanfacine with methylphenidate resulted in higher exposures to guanfacine and methylphenidate as compared to administration of both compounds alone, which was also reflected in the magnitude of pharmacological and some toxicological responses recorded. Combination treatment resulted in exaggeration of symptoms of treatment with guanfacine and methylphenidate alone. Next to the symptoms described for the therapies alone vocalisation and irritable behaviour was noted, shorter ulna length and slower balano preputial separation were seen. Also WBC count and number of lymphocytes, eosinophils and basophils were increased in females. For combination treatment the NOAEL is 0.3 mg/kg/day guanfacine and 16 mg/kg/day methylphenidate corresponding with exposure levels to guanfacine of 5.4 (m) and 9.09 (f) ng.hr/mL and to methylphenidate of 159 (m) and 331(f) ng.hr/mL on day 53 of age.

Other toxicity studies

The lack of local tolerance studies, antigenicity studies and phototoxicity studies is agreed.

Immunotoxicity

Changes in white blood cell parameters are reported. Incidental changes in WBC count are also seen in the clinical trials. Furthermore, in some studies spleen, thymus or lymph nodes were affected. Immune mediated idiosyncratic reactions should be monitored and reported in the PSURs.

Dependence

The Applicant reviewed the non-clinical and clinical literature relevant to the dependence potential of guanfacine. There are no data on self-administration of guanfacine, however, a considerable amount of data is available for clonidine, another well-known adrenergic α_2-agonist. The data on clonidine show that clonidine may induce self-administration in drug-naïve animals, but the pattern is distinct from amphetamine, cocaine, pentobarbital and morphine. In rats, clonidine variably substituted for opiates. These data show that clonidine may have some dependence potential, but the potential is considered to be low and the characteristics are different from well-known drugs of abuse.

Withdrawal studies mainly focussed on hemodynamic effects and guanfacine has been compared with clonidine. Whereas clonidine treatment may result in rebound effects after withdrawal, guanfacine generally does not.

Other studies showed that clonidine and guanfacine may reduce withdrawal symptoms after ethanol, opiate or diazepam withdrawal, but guanfacine was apparently less potent in this respect than clonidine.

The post-marketing experience with Intuniv in the USA does not indicate dependence potential, while during several decades of use as an antihypertensive drug, guanfacine has not emerged as a drug of abuse.

Taken together, it appears that the risk for dependence potential can be considered low. It is agreed that there is no need for additional non-clinical studies investigating dependence potential.

Impurities

Based on the provided study data and general toxicological considerations, the specified impurities are qualified up to the proposed limits.

2.3.4. Ecotoxicity / environmental risk assessment

Table 1 Summary of main study results

Substance (INN / Invented Name): guanfacine			
CAS-number (if available): 29110-47-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	log K_{ow} = 1.8	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.8	not B
Persistence	ready biodegradability	Waived, see OECD 308 study	
	DT50, parent	$DT_{50,\ water}$ = 8.7/11 d (l/l) $DT_{50,\ sediment}$ = 123/250 d (l/l) $DT_{50,\ system}$ = 15/17 d (l/l)	l=lake, DT50 values corrected to 12°C. Conclusion: P
Toxicity	NOEC	0.78 µg/L (daphnia)	T
	CMR	Not investigated	Potentially T
PBT-statement	guanfacine is considered not PBT, nor vPvB		
Phase I			

Calculation	Value	Unit			Conclusion
$PEC_{surface\ water}$, default F_{pen}	0.035	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 485, 435 L/kg $K_{oc\ soil}$ = 723, 441, 1180 L/kg			sludge (n=2) soil (n=3)
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308, parent	$DT_{50\ water}$ = 4.1/5.1 d (l/l) $DT_{50\ sediment}$ = 58/118 d (l/l) $DT_{50\ system}$ = 6.9/7.9 d (l/l) Sediment shifting >10% at or after 14 days			l = lake, DT50 values at 20°C; Significant shifting to sediment observed
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Pseudokirchneriella subcapitata*	OECD 201	NOE_rC	3.78	µg/L	growth rate
Daphnia magna. Reproduction Test	OECD 211	NOEC	0.78	µg/L	length
Fish, Early Life Stage Toxicity Test / *Pimephales promelas*	OECD 210	NOEC	0.94	µg/L	hatching; Ri = 3
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	2.8	µg/L	Unclear if sonication affected stability of guanfacine
Phase IIb Studies					
Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC	112	mg/kg	value normalised to 10% o.c.

Considering the provided data, the CHMP concluded that Intuniv was not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

Major non-clinical concerns were raised during the procedure concerning the carcinogenic potential of guanfacine as well as the uncertainties on the juvenile toxicity testing.

The Applicant was requested to review the available data relevant for assessing the risk for carcinogenic potential of guanfacine, especially with respect to pancreatic islet adenoma's, since these were present with an increased incidence in high dose males in a carcinogenicity study described in the FDA SBA for Tenex. It appeared that the increased incidence noted in this study can probably be explained by the increased survival leading to increased exposure times. The lack of any effect in females or in mice and the lack of any carcinogenic potential of other α2 AR agonists (clonidine, lofaxedine) gave further reassurance that the signal in the rat carcinogenicity study was unlikely to be of relevance for humans. The lack of any guanfacine-related tumorigenicity was also supported by post-marketing experience with Intuniv in the US. Therefore this issue was considered as resolved by the CHMP and routine monitoring of tumorigenicity after MA were considered sufficient as post-marketing surveillance

As Intuniv is indicated for children, juvenile toxicity studies with guanfacine were considered pivotal in this application. In the juvenile rat, guanfacine was rapidly metabolised and most of the parent compound had disappeared from circulation within half an hour. The slower clearance in humans and the prolonged release formulation proposed for Intuniv would lead to a significantly different exposure profile of guanfacine in humans. Cmax levels were, however still considerably in excess of human Cmax values.

Furthermore, despite these limitations, data from the juvenile toxicity performed suggested a potential to affect neurodevelopmental processes in early phases of brain development. Although such an effect cannot be excluded for the rat juvenile study, it is considered less likely that this would occur in children exposed from the age of 6 years, as the neurodevelopmental periods in the rat study and the age range in the intended patient population do not share the early developmental phases. As in other studies in the literature behavioural effects were reported when dosing was initiated at later stages, the observations are probably direct pharmacological effects. The finding in the juvenile toxicity study that the incidence and intensity of the behavioral signs increased during the late stages of the study may reflect a particularly sensitive period in these animals. The nature of the symptoms are also remniscent of overdose symptoms in pediatric patients This supported also that the observations may have been rather exaggerated pharmacological symptoms. Although definitive answers on neurodevlopmental perturbations could not be be draw from the juvenile study, the CHMP considered that behavioural symptoms that were observed were sufficiently discussed.

Further to the review of the non-clinical data, the CHMP considered also that further data were needed to characterise the pharmacological activity of metabolites. The MAH committed to further evaluate the pharmacological activity of the main metabolite 3-hydroxy guanfacine sulfate.

Furthermore, although the affinity for the receptor is much lower for the 5-HT2B receptor than for the α2A receptor, plasma concentrations of guanfacine after a maximal therapeutic dose are similar to EC50 values seen for guanfacine in functional in vitro assays evaluating the 5-HT2B receptor. Consequently, these data suggest there is a potential risk for developing valvulopathy.

In addition conflicting data and data gaps lead to uncertainty in the long-term cardiovascular safety with respect to the potential to induce QTc prolongation. The possibility of involvement of metabolites in a QTc prolongation liability may need to be considered if drug interaction leading to increased levels of metabolism intermediates is suspected.

ADME data, although limited, suggested approximately similar exposure to both metabolites in rats and to the most important metabolite, M13, in dogs. Since no proper AUCs were determined, this is no more than an rough estimate. Nevertheless, based on these data, it is concluded that most likely, exposure to the most important human metabolites has been similar to or lower than that in humans. So in the toxicity studies, like for the parent compound, there is no exposure margin for the major human metabolites. Requesting more data of improved quality would probably not result in a significantly different conclusion. Therefore, this was considered acceptable by the CHMP

Only literature data (mice) and summary data from the FDA SBA (rats and rabbits) on the reproductive toxicity were available. There are no or only very limited reported data on the use of guanfacine during pregnancy in humans. Potential strain specific teratogenicity is observed in mice, foetotoxicity in rat and rabbit. All effects seen in EFD studies were in the absence of proper toxicokinetic data. Preclinical findings and the lack of information on use of guanfacine in human during pregnancy lead to the conclusion that Guanfacine should not be used during pregnancy. This was reflected in the SmPC.

2.3.6. Conclusion on the non-clinical aspects

The CHMP considers that the non-clinical issues have been sufficiently addressed during the procedure. Overall, the non-clinical data were considered appropriate to support the proposed clinical use of guanfacine.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Applicant claimed that clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Analytical methods

The analytical methods used for determination of guanfacine in human plasma by the different facilities are well validated. The requested inter-laboratory analysis of the analytical methods was not performed and the applicant indicated that such analysis would not be possible for one out three analytical sites.

Plasma samples for incurred sample reanalysis for guanfacine were performed at Advion and Cedra, demonstrating incurred sample reproducibility for guanfacine. However, incurred sample reanalysis were not performed at Shire facility and the reliability of the analytical methods used at Shire has not been discussed as requested. As indicated in the PKWP document EMA/618604/2008 Rev. 6, one of the methods to indicate that the analytical methods is reproducible, is by interstudy comparison of the pharmacokinetic data. Across study comparison showed that pharmacokinetic parameters were comparable using samples analysed by all three analytical sites. Therefore, the absence of cross validation between the three analytical sites and the absence of incurred sample reanalysis at the Shire facility can be accepted

Absorption

As predicted in vitro, absorption of guanfacine in vivo was complete. The absolute bioavailability of immediate release guanfacine is 80%. Relative bioavailability of Intuniv as compared to immediate release guanfacine is 58%. Peak plasma concentrations are reached at 6 hrs. Administration of guanfacine with high fat meal resulted in 75 and 40% increase in Cmax and AUC, respectively. This significant food effect could be clinically significant, because many of the important adverse effects of Intuniv occurred in a dose-related manner. However, for the main Phase 3 studies in children with ADHD (SPD503-316, SPD503-312, and SPD503-315), the protocols did not provide specific instructions regarding food intake other than not to administer the drug with a high-fat meal Thus, it was agreed that Intuniv should not be taken with high fat meals.

Bioequivalence

The three different manufacturing sites utilizing different manufacturing processes, i.e. PII, SUMI/Owings Mills and DSM, were used during development programme. Based on the bioequivalence studies submitted, tablets manufactured at PII site are considered bioequivalent with tablets manufactured at SUMI/Owings Mills site, and tablets from SUMI/Owings Mills are bioequivalent with tablets from DSM, the final manufacturing site. The lack of direct bridging data for PII and DSM site is of little concern considering all comparative pharmacokinetic studies. However, tablets manufactured at PII site were used in the food effect study SPD503-104 and, shown below, there is a significant food effect and many important adverse events occur in the dose related manner. Based on this, it was necessary to know what is the food effect for the tablets from each blend manufactured at the final DSM facility. In the response, the applicant substantiated that the two manufacturing processes used PII and DSM site can be

considered as similar without any impact on the quality of the product and therefore a food effect study with a tablet manufactured at DSM site is no longer considered necessary.

The applicant confirmed that the batches used in studies 113 114, 114 and 1209A3111, are manufactured at SUMI site. Tablets from SUMI site were shown to be bioequivalent with tablets from DSM site, the final manufacturing site, and thus this issue was considered as resolved by the CHMP.

Distribution

Consistent with its lipophilicity and high permeability, guanfacine is largely distributed to the tissues with an apparent volume of distribution of 6.3 kg/L. According to literature, plasma protein binding of guanfacine is 70% and it is independed of drug concentration.

Elimination

Excretion

Based on the publication of Carchman et al, it can be concluded that biotransformation of guanfacine accounts for about 50% in the drug elimination, with a firs-pass of 20%. The total clearance of guanfacine was high, i.e. 414 ml/min (24 l/h), of which approximately 50% was renal. The ratio of renal clearance to creatinine clearance was 2.9 and 2.2 after oral and iv administration, respectively, indicating active secretion. Based on study SPD503-109 in 52 healthy volunteers, the elimination half-life was reported to be approximately 18 hrs.

Metabolism

The lack of a mass-balance study was considered as a significant deficiency in the dossier. The applicant identified 3-hydroxy guanfacine sulfate (M13) as a major circulating metabolite, representing a mean of 61% of the plasma radioactivity. However, it is unknown if this metabolite is active. This should be evaluated. Also in turn, an inhibition of sulfation of 3-OH guanfacine could lead to a substantial exposure to 3-OH-guanfacine, which pharmacological activity is unknown. Therefore, although in general phase II metabolites are not pharmacologically active, the applicant should evaluate that this holds also for 3-hydroxy guanfacine sulfate (M13), which represents substantial (60%) plasma radioactivity. The applicant should also investigate which enzymes are involved in the formation of 3-hydroxy guanfacine sulfate (M13) and discuss potential drug interactions that may affect the formation of this metabolite. If relevant interactions are anticipated, drug interactions affecting these pathways should be investigated in vivo. Increased exposure of the intermediate, 3-hydroxy guanfacineis not expected because 3-hydroxy guanfacinecan be metabolised by various pathways including sulaphatases and glucuronidases. If the sulphate conjugate contributes to the pharmacological activity, the elimination pathway of this metabolite should be investigated and potential interactions should be discussed. These studies could be performed as a post-approval commitment.

Consequences of possible genetic polymorphism

CYP3A4, the major metabolizing enzyme, is not associated with clinically important genetic variability.

Dose proportionality and time dependencies

Dose proportionality

Pharmacokinetics of guanfacine appeared to be dose proportional between 1 and up to the maximal recommended daily dose of 7 mg in the target population. In healthy volunteers, dose-proportional increase in Camx and AUC was demonstrated up to 4 mg, which was the highest dose tested in healthy adults. Thus, the pharmacokinetics of guanfacine can be considered as similar in children (aged 6 to 12) and adolescent (aged 13 to 17) ADHD patients, and healthy adult volunteers.

Time dependency

A formal evaluation of time-dependency, where the Ctrough values are measured over several days at steady state, were not provided. When comparing an extent of exposure at Day 14 and at Day 28, it seems that no auto-inhibition or auto-induction occurs.

Inter- and intra-subject variability

Intra- and inter-subject variability for the Cmax and AUC in healthy volunteers, children and adolescents is moderate.

Pharmacokinetics in target population (children and adolescents)

Fixed dose: After a single and multiple dosing, C_{max} and AUC were 35 and 25-30% higher, respectively, in children than in adolescents. CL/F in children was considerably lower than in adolescents. Higher exposure in children was most likely attributed to their lower body weight.

Weigh-based dose: In adolescents, following administration of 0.12 mg/kg dose, C_{maxss} and AUC_{ss}, were increased in the higher weight groups i.e. >50-70 kg and >70-90 kg vs. 30-50 kg group. Clearance decreased as weight increased. This difference was especially pronounced for the heaviest weight group (70-90 kg) as compared with the lowest weight group (30-50 kg). The mean maximal dose administered to the highest weight group was 9 mg, which explains higher exposure in this group. However, according to the proposed posology, the maximal daily dose for children weighing 58.5 kg and above is 7mg, which is expected to result in lower exposure.

Special populations

A population PK analysis were performed to evaluate the influence of different covariates on pharmacokinetics for guanfacine.

The model predicted that food significantly increases plasma exposure of guanfacine. This is conflicting with the applicant's conclusion on the food effect where similar exposure to guanfacine was seen at steady state under fasting conditions and after non high-fat meal. The predicted by the model food effect might have been overestimated including the data from study SPD503-203, in which a prototype formulation C was used for which guanfacine exposure is expected to be higher. Inclusion of this study possibly might have accounted for the high and unexpected variability for predicted CL/F, V /F, and ka. The applicant however did not address this issue and no changes were applied to the model. This issue is considered not resolved but it won't be further pursued. It should be noted however that for this reason and the fact that only four studies were included in the model building, the PK model is of a limited value and further re-evaluation of the model would be needed before its use in the future.

Gender and race

Gender and race were not found to be significant covariates in the PK model.

Weight

The model supported weight-based dosing with the exceptions of relatively heavy 6 year olds (40 kg) and 12 year olds (70 kg), which were expected to have lower plasma exposure, and of lightweight 12 years old expected to have higher plasma exposure. The applicant concluded that this finding is due to the higher variability caused by the limited number of subjects at the extremes of the age and weight ranges. This should not be an issue since patients are individually titrated based on effect. The exposure to guanfacine applying the dose recommendation as indicated in section 4.2 of the SPC, highly overlaps between different weight ranges, which support the cut-off point for these weight ranges.

Renal impairment

Based on the newly submitted mass-balance study with guanfacine prodrug, it was estimated that renal excretion is the major elimination pathway (80% of the radioactivity) with parent drug representing 30% of the urinary radioactivity, which is lower than initially estimated (50%). Based on the publication by Kirch et al 1980, there was a significant reduction in cumulative urinary excretion and renal clearance of guanfacine as the renal function decreased, though total body clearance of guanfacine was only slightly diminished. The elimination rate constant and elimination half live were however comparable between the three groups, which suggests increased hepatic elimination of the drug, though the metabolites profiles were not reported. There was however no clear trend towards difference in plasma exposure in as the renal function decreased. This finding could be attributed to the parallel renal and metabolic routes of elimination minimizing the effects of diminished renal function but also to the low number of subjects available for plasma analysis. Although the data on guanfacine plasma exposure is inconclusive, considering that dosing should be individualized according to the therapeutic needs and response of the patient (section 4.2), it can be agreed with the applicant's proposal that the dose reduction may be necessary in subjects with severe renal impaired, but also in subjects with an end stage renal disease or requiring dialysis.

Hepatic impairment

Hepatic metabolism accounts for at least 50% in the drug elimination and therefore it is expected that hepatic impairment will result in marked increase in guanfacine exposure. Since it is not expected that guanfacine would be used in children and adolescents with impaired liver function and since dosing is to be individualized, it is agreed with the applicant's proposal that the dose reduction may be necessary in subjects with impaired renal function. However, the dose reduction should concern all degrees of hepatic impairment and not only severe.

Elderly

Guanfacine is not indicated for the use in elderly.

Pharmacokinetic interaction studies

In vitro interactions

Influence of other drugs on pharmacokinetics of guanfacine

P-gp: Guanfacine was shown to be a drug with a high permeability that is transported through the Caco-2 cell monolayers by the passive pathway. Guanfacine was not considered a substrate for the P-gp pump. Therefore, interactions at P-gp level can be excluded.

Cytochrome P450: Assays in both pooled microsomes and Supersomes confirmed the major involvement of CYP3A5 in guanfacine metabolism. In vivo, a significant interaction with strong CYP3A4 inhibitor and inducer was shown (see below). Involvement of other CYP isoenzymes, if any, is thought to be insignificant.

Considering that metabolism accounts for more than 50% in the drug elimination, the in vitro studies identifying transporters involved in hepatic uptake are necessary and the applicant committed to perform such studies post-approval. In addition, when a candidate transporter has been identified, an in vivo study with a strong inhibitor/inducer of the transporter at the site of interest is recommended, if feasible (see chapter 5.2.4.of the EMA guideline on drug-drug interactions). Renal excretion is the major elimination pathway (80% of the radioactivity) with parent drug representing 30% of the urinary radioactivity, based on the newly submitted mass-balance study. Guanfacine was found to be a substrate for OCT2 transporter and OCT2- mediated uptake of guanfacine (Li et al 2014) and the genetic polymorphism of OCT2 has been described in the literature (Yoon et al. 2013). However, at the worst case scenario, an inhibition of OTC2-mediated transport of guanfacine would result in 30% increase in

guanfacine exposure, which is not considered clinically relevant. Therefore, in vivo interactions with OCT2 inhibitor or in vivo evaluation of OCT2 genetic polymorphism are not warranted. For the same reason, interactions with drugs that may decrease or increase the renal elimination of guanfacine are not expected to result in a clinically relevant increase in guanfacine exposure.

Effect of guanfacine on pharmacokinetics of other drugs

P-gp: At clinically relevant concentrations, guanfacine was not shown to be an inhibitor of p-gp mediated transport of other drugs.

CYP inhibition: Guanfacine is not considered to be a reversible inhibitor of CYP1A2, 2C9, 2C19, 2D6 and hepatic 3A4/5. No conclusion on time depended inhibition (TDI) of CYP1A2, 2C9, 2C19, 2D6 and hepatic CYP3A4/5 can be made, as the pre-incubation time of 15 min is considered too short. In the time dependency experiments, at least 30 min of pre-incubation and IC50 shifts calculations are preferred. The applicant will re-evaluate TDI of CYP1A2, 2C9, 2C19, 2D6 and hepatic 3A4/5 as a post-approval commitment.

Guanfacine is not considered to be a reversible or mechanism-based inhibitor of CYP2C8 at clinical concentrations. Inhibition data towards CYP2B6 and it will be provided in as a post-approval commitment.

No conclusion on inhibition of intestinal CYP3A4 can be made as the highest concentration used i.e 3.5 µM was below maximal expected intestinal exposure to guanfacine of 10 µM. The applicant will perform the inhibition studies towards intestinal CYP3A4, in line with the guideline on drug-drug interaction recommendations (e.g. inclusion of strong inhibitor, maximal intestinal exposure of the drug,i.e.10 µM, pre-incubation time of at least 30 min together with IC50 shift calculation is recommended in case of TDI) as post-approval commitment.

Transporters: The Applicant will provide inhibition information for the transporters BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1 andOAT3 for the parent drug as a post-approval commitment. The lack of inhibition studies for BSEP, MRP2 and MATE1 and MATE2 has been justified.

CYP induction: No conclusion on guanfacine induction potential towards CYP enzymes can be made as the design of the CYP induction study is not considered adequate i.e the incubation period of 2 days used in the study is considered too short as evident from failed or weak responses from the control inducers assays. Incubation time of 3 days is recommended. The applicant will conduct such a study as post-approval commitment.

UGT inhibition: Guanfacine and 3-hydroxy-guanfacine, at clinically relevant concentrations have no potential for clinically significant UGT-mediated drug-drug interactions. There was no sign of an interaction with valproic acid. However, the literature indicates that guanfacine increases plasma concentration of valproic acid. Plasma valproate levels rapidly increased when guanfacine was co-administered decreased by 41% after guanfacine was tapered and discontinued*. The authors proposed that the mechanism behind this interaction may involve competition at the level of hepatic glucuronidation, although shifts in protein binding cannot be ruled out. The proposed wording in section 4.5 of SmPC to monitor plasma levels of valproic acid when co administered with guanfacine and to consider a dose adjustment of either one, was agreed by the CHMP.

In vivo interactions

Ketoconazole: Co-administration with strong CYP3A4 inhibitor, ketoconazole, resulted in 2 and 3 fold increase in guanfacine Cmax and AUC, respectively. Adequate dosing instructions have been described when moderate and strong CYP3A4 inhibitors are co-administered with Intuniv.

Rifampin: Co administration with CYP3A4 inducer, rifampin, resulted in 50 and 70% decrease in Cmax and AUC respectively. According to section 4.5, an increase of Intuniv dose should be considered. Adequate dose recommendation is provided when Intuniv is co-administered with CYP3A4 inducers.

Methylphenidate: No pharmacokinetic interaction was observed between guanfacine and methylphenidate. This is expected considering different elimination pathways of the drugs i.e methylphenidate is not metabolized by the CYP450, nor methylpenidate is an inducer nor inhibitor of the cytochrome P450 system.

Lisdexamfetamine dimesylate: When coadministered with lisdexamfetamine dimesylate, guanfacine Cmax increased by 19%, while the AUC remained unchanged. However, this observed slight increase in guanfacine Cmax when co administered with lisdexamfetamine dimesylate is not considered to be clinically significant.

In conclusion, the following remaining PK issues which need to be addressed in post-authorisation studies are as below:

In order to identify the transporter involved in hepatic uptake, the MAH should perform and provide results of in vitro studies identifying transporter involved in hepatic uptake considering that metabolism accounts for more than 50% in the drug elimination.

In addition, when a candidate transporter has been identified, an in vivo study with a strong inhibitor/inducer of the transporter at the site of interest is recommended, if feasible (see chapter 5.2.4. of the EMA guideline on drug-drug interactions)

In order to identify if guanfancine is an inhibitor of CYP enzymes and drug transporters, the MAH should re-evaluate, conduct and provide the results of a Time Dependent Inhibition study for the following:

- CYP1A2, 2C9, 2C19, 2D6 and hepatic 3A4/5;

- CYP2B6;

- Intestinal CYP3A4, in line with the guideline on drug-drug interaction recommendations (e.g. inclusion of strong inhibitor, maximal intestinal exposure of the drug,i.e.10 µM, pre-incubation time of at least 30 min together with IC50 shift calculation is recommended in case of TDI);

- Transporters BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3.

In order to identify if guanfancine can induce CYP enzymes, the MAH should re-perform the CYP induction study in line with the current EMA guideline on drug-drug interaction.

In order to evaluate the pharmacological activity of 3-hydroxy guanfacine sulfate, the MAH should evaluate the pharmacological activity of 3-hydroxy guanfacine sulfate by in vitro assays. If 3-hydroxy guanfacine sulfate shows pharmacological activity in vitro, the enzyme involved in its formation should be identified.

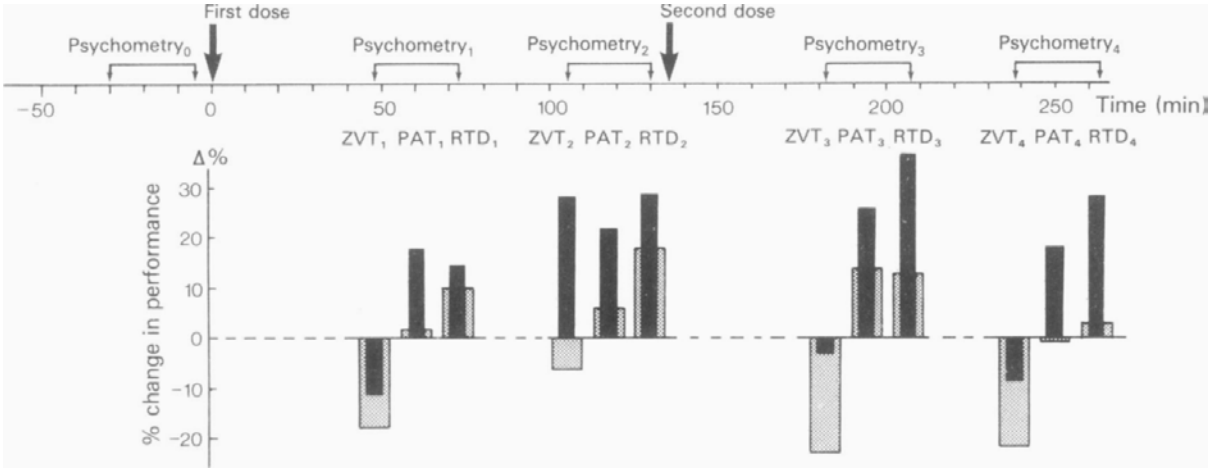
2.4.3. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

Based on a review of published findings in rodents and higher species, the applicant states that: [guanfacine, like the other α2-adrenoceptor agonists, is sedative]…[this potential side-effect in man is entirely consistent with guanfacine's known pharmacology as a moderately potent and selective α2A-adrenoceptor agonist.] No studies in healthy volunteers were performed by applicant to study effects

of guanfacine on the central nervous system (CNS). The applicant refers to a published study by Kugler et al (1988) who measured EEG's, subjective well-being, cognitive performance, plasma noradrenaline levels and effects on blood pressure in 24 healthy students before and after 2 doses of guanfacine (1.0 /2.0mg) or clonidine (0.15 /0.3mg) with a 2-hour interval. Effects on blood pressure were reported to be similar, but guanfacine had less suppressive effects on plasma noradrenaline, self-reported wellbeing, measures of cognitive performance and EEG activity. Regarding effects on cognitive performance, the figure below shows mean results for guanfacine (grey columns) and clonidine (black columns) for: (1) the ZVT ('Zahlen Verbindings Test', Oswald 1978) which tests time needed for sorting of 24 randomly arranged numbers, (2) the PAT ('Pauli Adding-up Test', Arnold 1961): time needed for adding 2 numbers, and (3) the RTD ('Reaction Time Test', Mierke 1956): proportion of correct recognition of color signal within 0.8 seconds. In this study, limited information is available regarding statistical testing of change of performance within treatments. Regarding guanfacine, improvement of RTD-performance was significant ($p<0.005$) at the first post-dose measurement as compared to baseline. The possible improvement of PAT-performance at the third post-dose measurement tested non-significant as compared to baseline. Mean (sd) ZVT-response times were: baseline: 26.6±7.5; period 1: 21.9±8.8; period 2: 24.2±9.4; period 3: 20.6±5.8; period 4: 20.9±3.3.



A dose-response study in 31 ADHD-patients 13-17 years of age showed decreased systolic and diastolic blood pressure, but a (rebound) increase of approximately 5-7 mmHg with a maximum at 5 days post-dose. At 1, 3, and 5 minutes after standing up, blood pressure decreased in a dose-dependent fashion. Also a dose-dependent slowing of heart rate was shown, lowering pulse to a minimum of approximately 50 bpm at 4 hours post-dose and onwards.

A thorough-QT study was performed to assess the risk of arrhythmia associated with guanfacine-treatment. A total of 58 healthy adult volunteers were treated with immediate-release guanfacine up to 6 mg twice daily and 8 mg once daily (day 6), placebo and active control moxifloxacin 400mg. A QT-interval prolongation of >10ms was included in the confidence bounds of guanfacine at 12 hours post dose. A similar comparison was performed using individually collected heart-rate correction factors. Using those corrections, guanfacine was not associated with clinically relevant QT-interval prolongation.

In post-hoc analyses of time-points beyond 12 hours post-dose, QT-intervals at time points through 24 hours were assessed. In those analyses the corrected QT-intervals included a 10 ms prolongation as compared to placebo in the 95%-confidence interval, both using the fixed 'Friderica'-correction and the individually ascertained correction factors. The applicant considers these post-dose prolongations: '…reflective of changes in autonomic tone occurring as a result of decreasing systemic guanfacine concentrations following 6 days of high dose guanfacine.'

No data were submitted regarding pharmacodynamic interactions with other medicinal products or substances. Also, no data were submitted regarding genetic differences in PD response.

2.4.4. Discussion on clinical pharmacology

The three different manufacturing sites utilizing different manufacturing processes, i.e. PII, SUMI/Owings Mills and DSM, were used during development programme. Based on the bioequivalence studies submitted, tablets manufactured at PII site are considered bioequivalent with tablets manufactured at SUMI/Owings Mills site, and tablets from SUMI/Owings Mills are bioequivalent with tablets from DSM, the final manufacturing site. The lack of direct bridging data for PII and DSM site is of little concern considering all comparative pharmacokinetic studies. However, tablets manufactured at PII site were used in the food effect study -104 and, shown below, there is a significant food effect and many important adverse events occur in the dose related manner. The applicant clarified during the procedure what the food effect is for the tablets from each blend manufactured at the final DSM facility.

The applicant clarified that the batches used in studies 113 114, 114 and 1209A3111, are manufactured at SUMI site. Tablets from SUMI site were shown to be bioequivalent with tablets from DSM site, the final manufacturing site, and thus this issue was considered as resolved by the CHMP.

At the moment, it is unknown whether any pharmacologically active or toxic metabolites are formed in humans. If such metabolites are formed in humans, enzymes contributing to main formation and elimination pathways of these metabolites should also be identified. This will be further investigated by the company as a pharmacokinetics study is requested accordingly and is part of the pharmacovigilance plan in the risk management plan.

According to section 5.2 of the SmPC, the pharmacokinetics of guanfacine is similar in children (aged 6 to 12) and adolescent (aged 13 to 17) ADHD patients, and healthy adult volunteers. However, in healthy volunteers, after multiple dosing, AUC and Cmax increased in a dose-proportional manner up to 3 mg dose and more than dose-proportional between 3 and 4 mg dose, based on study 1209A311. The applicant is asked to discuss this further. During the procedure the applicant was requested to further evaluate dose-proportionality up to the highest, 7 mg, dose in children and adolescents using PK model.

Weight was found to be the main predictor of guanfacine pharmacokinetics in the PK model. The model supported weight-based dosing with the exceptions of relatively heavy 6 year olds (40 kg) and 12 year olds (70 kg) which were expected to have lower plasma exposure, and of light weight 12 years old expected to have higher plasma exposure. This finding was explained by the applicant during the procedure. The applicant was asked to reanalyse the data with the refined model. In addition, it was not clear what the cut-off points for different weight groups in posology were based upon. The exposure to guanfacine applying the dose recommendation as indicated in section 4.2 of the SPC, highly overlaps between different weight ranges, which supported the cut-off point for these weight ranges.

Interactions, CYPs mediated and transporter mediated, should further be elucidated. This will be investigated as post-approval measures commitments.

Effects of guanfacine on vital functions were sufficiently studied in the past. Lowering of blood pressure and heart rate by guanfacine is considered to be related to the mechanism of action and may be hazardous in treated patients regarding risk of syncope and falls. This was considered as the CHMP as a major safety concern (see section on safety assessment).

Regarding the 12-hours post-dose measurement of effects on cardiac conductivity the following can be concluded: the 10ms QT-interval prolongation cut-off was included in the 95% confidence bounds of guanfacine-treatment associated prolongations at 12 hours post dose when calculated using the Fridericia, but not the individually ascertained correction factors. Regarding individual ECG-derived correction factors, as outlined in the guideline (Topic E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Antiarrhythmic Drugs), ECG-measurements may be inaccurate during rapid heart-rate changes due to the 'QT/RR hysteresis effect'. As guanfacine has a pronounced effect on heart rate, possibly including rapid heart rate changes, that effect may induce

overcorrection by using individually ascertained correction-factors, possibly obscuring a clinically relevant true prolongation of the QT-interval. Therefore the Fridericia-corrected QT-intervals are considered more reliable, by not overcorrecting for heart-rate (-variability). As Fridericia-corrected QT-intervals include the 10ms prolongation at 12 hours post-dose, guanfacine may be associated with risk of arrhythmia. The 12-hour time point falls well after Tmax of guanfacine immediate release that was used in the study. The effect may be more pronounced using prolonged-release guanfacine that is subject to the current application.

In the post-hoc analyses of the thorough QT-study, QT-interval prolongations were confirmed for later (i.e. >12 hours) post-dose time-points using both fixed ('Fridericia') and individually derived correction factors. This finding suggests 24 hour post-dose rebound-prolongation of QT-intervals, with associated risk of arrhythmia. Applicant states that in the 12-24 hour post-dose timeframe, actual QT-intervals were decreasing, indicating reduced risk of TdP. However, this explanation is considered contradictory to the justification of use of (fixed or individual) correction factors at earlier time-points that reduce QT-intervals, thereby suggesting low risk of arrhythmia. In the final discussion the applicant disqualifies both the fixed correction factor and the individually derived correction factors. The applicant discussed also satisfactorily possible subgroups of patients with enhanced vulnerability for adverse effects of guanfacine due to genetic differences.

2.4.5. Conclusions on clinical pharmacology

The three different manufacturing sites utilizing different manufacturing processes, i.e. PII, SUMI/Owings Mills and DSM, were used during development programme. There is a significant food effect for the tablets manufactured at PII site. Since there is no bioequivalence study between PII and the final manufacturing DSM site, the food effect for the tablets from each blend manufactured at the final DSM facility was further evaluated during the procedure and this issue was considered as resolved by the CHMP.

The metabolism of guanfacine in humans as well as interaction potential was further elucidated during the procedure.

Weight was found to be the main predictor for guanfacine pharmacokinetics in the PK model. The model supported weight-based dosing with the exceptions of relatively heavy 6 year olds (40 kg) and 12 year olds (70 kg) which were expected to have lower plasma exposure, and of light weight 12 years old expected to have higher plasma exposure. The applicant was asked to reanalyze the data with the refined model. In addition, the applicant was asked to model the exposure to guanfacine in the different weight groups according to the proposed posology, as it was not clear what the cut-off points for different weight groups in posology were based upon.

The effects of guanfacine in healthy volunteers regarding blood pressure and heart rate are detected both for immediate (decrease) and rebound (increase) effects. These effects are dose-dependent and can be linked to the mechanism of action of guanfacine on vascular tone and heart action. These findings suggest risk of syncope, falls, and accidents. Risk of accidents may be more pronounced in children and adolescents diagnosed with ADHD, who a priori may be accident-prone due to symptomatology of the underlying disorder. These risks may be serious, and are confirmed in the safety-analysis of the clinical treatment studies. This was considered to be a major objection by the CHMP during the procedure (see section 3: 'Clinical safety').

In the course of the procedure, the applicant provided an overview on the current treatment options with the knowledge available so far on the mechanism of action of methylphenidate and amphetamine (classified as stimulants) and atomoxetine (classified as non-stimulant) and elaborated on the advantage of the availability and implications of having different treatment options for ADHD. It is claimed that SPD503 does not act on presynaptic dopamine and norepinephrine transporters, however it does act on presynaptic α2 adrenoreceptors (α 2A, α 2B, α 2C) through which it exerts a sedative effect. The main effect on ADHD is believed to be through direct stimulation of post-synaptic α 2A receptors, which should lead to improved prefrontal cortical regulation of attention, behaviour and emotion. Some proof for this MOA is provided from data in spontaneously hypertensive rats and the publication of Bedard et al, 2015

about changes in right midcingulate cortex/supplementary motor area and left posterior cingulate cortex in ADHD subjects.

The issues pertinent to the Pharmacokinetic aspects of intuniv were clarified during the procedure.

The CHMP was of the view that the available information in the scientific literature as well the PK data collected in the clinical trials were sufficient to support the application for Intuniv in the treatment of ADHD from a clinical pharmacology perspective.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Altogether, the clinical development plan included 13 phase 2-3 studies with guanfacine in children and adolescents with ADHD. These included:

- 5 primary efficacy studies
    - 2 short-term dose-response studies (301, 304)
    - 2 short-term flexible dose studies (312, 316)
    - 1 randomised withdrawal study (315)
- 8 supportive studies
    - 3 long-term open label extension studies 303, 305, 318(ongoing)
    - 1 placebo controlled (PC) study in children with ADHD and oppositional symptoms (307)
    - 2 studies (1 PC) of guanfacine in combination with psychostimulants (313, 205)
    - 1 PC study with guanfacine administered either in the morning or in the evening (314)
    - 1 PC study with the aim to assess effect of guanfacine compared with placebo on cognitive tasks (206)

The design of the pivotal studies are summarised in the table below.

Table 2 Design of the pivotal studies

Study ID / year	No. of study centres / locations	Design	Study Objective	Study Posology	Subjs by arm entered/compl.	Duration	Gender M/F Mean Age (Range)	Diagnosis Incl. criteria	Primary Endpoint
Dose-response studies									
301/ 2003	48/US	R,DB, PG,PC	Safety and Efficacy	2mg 3mg 4mg Placebo	87/58 86/55 86/49 86/53	3wk titrat. 2wk maint. 3wk taper	257/88 10.5 (6-17)	ADHD DSMIVTR	ADHD-RS-IV (investigator)
304/ 2004	51/US	R,DB, PG,PC	Efficacy	1mg 2mg 3mg 4mg Placebo	62/45 65/47 65/38 66/40 66/41	3wk titrat. 3wk maint. 3wk taper	233/89 10.5 (5-17)	ADHD DSMIVTR	ADHD-RS-IV (investigator)
Flexible Dose studies									
316/ 2001-2013	58/US, Canada EU	R,DB, PG, PAC	Efficacy	1-7mg Placebo Atomoxetine 40-100mg	115/90 111/92 112/87	4-7 wk opt 6 wk maint 2 wk tapr.	249/88 10.8 (6-17)	ADHD DSMIVTR	ADHD-RS-IV (investigator)
312/2001-2013	52/US	R,DB, PG,PC	Efficacy	1-7mg Placebo	157/105 157/102	7 wk opt 6 wk maint 2 wk tapr.	202/110 14.5 (13-17)	ADHD DSMIVTR	ADHD-RS-IV (investigator)
Randomised withdrawal study									
315/2010-2013	58/US, Canada, EU	RW,DB, PG,PC	Maintenance of efficacy	1-7mg Placebo	157/72 159/49	13 wk open 26 wk rand. With. 2 wk tapr.	396/130 10.7 (6-17)	ADHD DSMIVTR	Proportion Tx failures

R=Randomised; DB=Double Blind; PG=Parallel Group; PC=Placebo Controlled; PAC=Placebo and Active Controlled; RW=Randomised Withdrawal

As the table indicates, the pivotal studies included 2 short-term (5 weeks+ 3 weeks taper) dose response (1-4 mg) studies, 2 short-term (13 weeks + 2 weeks taper) flexible dose (1-7mg) studies, and 1 randomised withdrawal study with a 26 randomised withdrawal phase. Included patients were at the age range of 6-17, except study 312 which included only adolescents (13-17). In addition, patients were required to meet DSM-IV-TR criteria for a primary diagnosis of ADHD. Oppositional Defiant Disorder (ODD) was a permitted comorbid disorder.

One study (study 316) included an active controlled arm. Two of the studies included EU centers (studies 316 and 315). In addition to the primary endpoint, an ADHD symptom rating scale (ADHD-RS-IV), 3

studies included a functional measure (studies 312, 316, and 315), which is a requirement in ADHD studies, i.e. it is required to demonstrate improvement not only on ADHD symptoms but also on social functioning, as dysfunctioning (in school, family or in social situations) is an integral part of the ADHD diagnosis.

Results with respect to patients disposition showed high dropout rate, especially in the randomised withdrawal study (52% in the active arms and 67% in the placebo arm). The most frequent reason for dropout in the guanfacine arm was treatment failure (30% out of the total of 52%) and most occurred in the first month of treatment.

The following table summarise the primary efficacy results from the main studies.

Table 3. Summary of primary efficacy ADHD-RS-IV for the ITT population

Study	Tx groups	N	Baseline ADHD-RS-IV (SD)	Change from baseline (SD)	Difference from placebo (95%CI) *Effect size*	Responders*	Difference from placebo (95%CI)
Dose-response studies							
301	2mg	84	38.1 (9.3)	-15.4 (12.8)	6.5 (2.5 , 10.5) 0.5	Not provided	
	3mg	82	36.1 (10.1)	-15.8 (13.0)	6.9 (2.9,10.9) 0.5		
	4mg	81	36.8 (8.7)	-19.0 (13.7)	10.1 (6.0, 14.2) 0.8		
	Placebo	78	38.4 (9.2)	-8.9 (12.9)	NA		
304	1mg	57	41.7 (7.81)	-20.4 (14.0)	8.2 (3.4,13.1) 0.6	73.7%	16.6% (-0.1 ; 33.3)
	2mg	63	39.9 (8.74)	-18.0 (14.9)	5.8 (0.9,10.7) 0.4	69.8%	12.7% (-4.0 ; 29.4)
	3mg	60	39.1 (9.22)	-19.4 (14.6)	7.2 (2.3,12.1) 0.5	75.0%	17.9% (1.5 ; 34.3)
	4mg	63	40.6 (8.57)	-20.9 (11.9)	8.7 (4.4,13.1) 0.7	81.0%	23.9% (8.3 ; 39.5)
	Placebo	63	39.3 (8.85)	-12.2 (13.0)	NA	57.1%	NA
Flexible Dose studies							
316	1-7mg	114	43.1 (5.5)	-23.9 (12.4)	-8.9 (-11.9, -5.8) 0.7	64.3%	21.9% (9.2 ; 34.7)
	AtomoxetinePlacebo	112	43.7 (5.9)	-18.6 (11.9)	-3.8 (-6.08,-0.7) 0.3	55.4%	13.0% (0.0 ; 26.0)
		111	43.2 (5.6)	-15.0 (13.1)	NA	42.3%	NA
312	1-7mg	155	39.9 (5.57)	-25.7 (10.1)	6.2 (3.7,8.7) 0.5	66.9%	21.1% (10.3 ; 31.9)
	Placebo	157	40.0 (6.11)	-19.5 (12.6)	NA	45.8%	NA
Randomised withdrawal study							
						% Tx failure	**Difference from placebo (95%CI)**

315	1-7mg	150	43.5 (6.3)	9.6 (11.5)	-6.3 (-9.2,-3.4)	49.3%	-15.6% (-26.6 ; -4.5)
	Placebo	151	43.5 (6.3)	15.9(14.2)	[0.5] NA	64.9%	NA

R=Randomised; DB=Double Blind; PG=Parallel Group; PC=Placebo Controlled; PAC=Placebo and Active Controlled; RW=Randomised Withdrawal

* In study 304 response was defined as ≥ 25% reduction from baseline in the ADHD-RS-IV score. In the flexible dose studies (312 and 316), response was defined as a ≥30% reduction from baseline in the ADHD-RS-IV total score and a CGI-I of 1 or 2.

Results for the PP population were consistent with those for the ITT population.

Mean effect sizes in the short-term studies were, Study 301: 0.4; Study 304: 0.5; Study 316: 0.7; Study 312: 0.5. Overall effect size was 0.5. This effect size seems smaller than the one usually seen for MPH. A meta-analysis of 62 randomized studies of MPH in children and adolescents Schachter et al (2001) found effect sizes of 0.8 for teacher's ratings and 0.5 for parents ratings. In a meta-analysis of 8 randomized studies of MPH in adolescents Smith et al (2000) found a mean effect size of 0.9. These effects are larger than the mean effect size of 0.5 found for Guanfacine in this dossier. However, the effect size of guanfacine (0.7) in study 316 is larger compared to the effect size of atomoxetine (0.3).
The difference in responders between guanfacine and placebo is in the range 13%-24% across the short-term trials, which is acceptable. However, the CHMP noted that the responder's definition was not provided á priori in the study protocols.

Furthermore, the results across all pivotal studies showed an inconsistent effect in adolescents. In the mixed age group studies (301, 304, 316 and 315), no effect in adolescents was demonstrated leaving study 312 as the only study where an effect in adolescents was demonstrated. The company was requested to clarify this point and was able to provide a number of plausible reasons, including doses that are too low (in the fixed dose studies), small samples, and high placebo response (studies 316 and 315). These explanations and the fact that similar efficacy to that obtained in children was demonstrated in the adolescents study (312); a mean effect size identical to the effect obtained in children (0.5) and a comparable difference from placebo in responder rate (21%), sufficiently support the efficacy of guanfacine in adolescents with ADHD. Furthermore the applicant provided some additional reassurance with data on long-term efficacy in adolescents generated in the ongoing open label study INTUNIV-318. The mean change from baseline after month 6, 12 and 18 in the ADHD-RS-IV total score was comparable between children and adolescents, despite the fact that baseline scores in the children were higher. The proportions of adolescents who were rated as normal to borderline mentally after 6, 12 and 18 months were respectively 72.2%, 76,3% and 87,0% and were higher than the proportions in the respective children groups . All together these preliminary long term data provided some reassurance that a long term effect of guanfacine on ADHD could be expected and that this might translate into a reasonable proportion of subjects being defined as "normal or borderline mentally ill". This may be considered as a relevant achievement in the management of ADHD adolescents.

Results by ADHD subtypes (inattentive or combined) were presented in the fixed dose studies (301 and 304). The results showed that the effect was larger and statistically significant only for the combined subtype but not for the inattentive subtype. Importantly, this was not due to smaller numbers in the inattentive subtype but to smaller effect size. This suggested that sedative effects contribute to the effect of Guanfacine.

To address this issue the Applicant provided analyses stratified for the patients who did or not report sedation as an AE (for fixed dose studies 301 and 304 and flexible dose studies 312 and 316).

In the pooled data from studies 301 and 304 the effect size in the subgroup with sedative AEs was smaller than in the subgroup without sedative AEs (0.17 vs 0.49 respectively). The Applicant explained this as probably due to the high placebo response in this subgroup. While this was acknowledged by the CHMP as a plausible explanation, there were some reservations expressed with respect to the fact that the high(er) placebo response in the subgroup with sedative AEs may support the hypothesis that (at least part of) the effect is due to sedation.

However, additional analyses do not support this hypothesis. Drop outs in the two subgroups (with and without sedative AEs) were similar. The proportion of responders increases with time while sedative AEs occurred mainly in the first weeks of treatment.

In addition, the data from the randomized withdrawal study 315 was analysed according to sedative AES. The groups were balanced in the sense that 54.7% with sedative AEs were randomized to INTUNIV and 53.6% were randomized to the placebo group. The analysis on the primary endpoint i.e. cumulative treatment failure rate (≥50% increase (worsening) in ADHD-RS-IV Total Score and a ≥2 point increase (worsening) in CGI-S compared with respective scores at 2 consecutive visits) showed that in the subgroup with sedative AEs there was a higher but not statistically significant treatment failure rates in the placebo treated vs INTUNIV treated subgroup (66.7% vs 53.7%); in the subgroup without sedative events the difference was again in favour of INTUNIV but also not statistically significant (62.9% vs 44.1%). Also the treatment effect sizes were comparable between the subgroup with and without sedative AEs (0.47 and 0.51 respectively).

The additional data show that an efficacy on ADHD symptoms has been observed also in the subjects without reported sedation and also no clear temporal relationship between efficacy and reporting of this AE. This suggests that efficacy may be achieved at least partially via a different mechanism of action, although contribution of sedation to the reduction on the symptom scale cannot be completely excluded. Effects on the inattentive and hyperactive subscales were also shown to be of similar magnitude which was also in favour of a true effect on the core symptoms of ADHD rather than the results of sedation only.

In study 316, a significant effect was obtained in both continents (EU and N. America) while in study 315 (the randomised withdrawal study) only results in the EU were statistically significant. This is mainly due to a larger placebo response among N. American patients. In any case, results presented in this dossier do not seem to be driven by positive results in the N. American study population and hence there was no reason for concern in this respect.

With regard to the effect on functioning, the analysis on the data from studies 312 and 316 showed a numerical trend for improvement relative to placebo on the WFIRS P Global score, Family score, and School and Learning score in both the subgroup with and without sedative AEs. The higher scores observed in the subgroup without sedative AEs indicate that sedation has a negative effect on functioning, which is not unexpected.

Results on the functioning measure are presented in the table below.

Table 4. Summary of secondary efficacy WFRIS (measure of functioning)

Study	Tx groups	N	Baseline WFIRSP		Change from baseline (SE)		Difference from placebo (95%CI)	
			Learning &school	Family	Learning &school	Family	Learning &school	Family
Flexible Dose studies								
316	1-7mg	114	1.39	1.41	-0.64 (0.5)	-.62 (.6)	-0.22 (-0.36 ; -0.08)	-0.21 (-0.36 ; -0.06)
	Atomoxetine	112	1.40	1.48	-0.58 (0.5)	-0.50 (.6)	-0.16 (-0.31 ;-0.02)	-0.09 (-0.24 ; 0.06)
	Placebo	111	1.37	1.44	-0.42 (0.5)	-0.41 (.6)		
312	1-7mg	155	1.29	1.01	-0.57 (0.7)	-0.37 (0.6)	-0.12 (-0.25 ; 0.02)	-0.06 (-0.19 ; 0.08)
	Placebo	157	1.30	0.91	-0.46 (0.6)	-0.31 (0.6)		
Randomised withdrawal study								
							Difference from placebo (95%CI)	
315	1-7mg	150	0.74	0.73	0.24	0.24	-0.14 (-0.26 ; 0.01)	-0.08 (-0.20 ; 0.05)
	Placebo	151	0.68	0.70	0.38	0.31		

R=Randomised; DB=Double Blind; PG=Parallel Group; PC=Placebo Controlled; PAC=Placebo and Active Controlled; RW=Randomised Withdrawal

As the table indicates, statistically significant results with respect to functioning were only observed in study 316 but not in studies 312 and 315.

Clinical studies in special populations

Study 307 was a randomized, double-blind, multi-center, flexible-dose, placebo-controlled, dose-optimization study in children aged 6-12 years with symptoms of oppositionality and a diagnosis of ADHD (n=217). The purpose of this study was to examine the effect of guanfacine on oppositional symptoms, as measured by the change from baseline score on the oppositional subscale of the CPRS-R:L.

Results show statistically significantly ($p \leq 0.05$) greater mean reductions at endpoint from Baseline (indicating improvement) in oppositional subscale of CPRS-R: L scores in the guanfacine group compared to placebo (10.9 points vs. 6.8 for guanfacine vs. placebo, respectively) and the effect size was 0.6 ($p<0.001$). These reductions represent a percentage reduction of 56% vs. 33% for guanfacine vs. placebo, respectively.

Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

Supportive studies

Several randomized, double-blind, multi-center, placebo-controlled supportive studies were conducted.

- Study 206 (n=182) was designed to assess the effect of guanfacine (1, 2, and 3mg) on cognitive function, in children and adolescents aged 6-17 years diagnosed with ADHD.

Results showed that cognitive functioning such as reaction time and sustained attention did not improve significantly following treatment with Guanfacine compared with placebo.

Although this was a safety study intended to demonstrate that Guanfacine has no adverse effects on cognitive functioning, results reinforced the need to further evaluate the effect on cognitive functioning of guanfacine.

- Study 313 was an add-on of guanfacine (1, 2, 3, and 4mg/day) when co-administered with long-acting psycho-stimulants in partial responders (6-17). Suboptimal response was defined as an ADHD-RS-IV total score of ≥24 and a CGI-S score ≥ 3 at screening and baseline. The results showed that patients treated with add-on guanfacine improved more on the ADHD-RS-IV compared to those treated with add-on placebo (20.7 (12.6) points vs. 15.9 (11.8); difference: 4.9 95% CI 2.6 , 7.2)). No age differences were observed with respect to response to the ADHD-RS-IV. The study did not include a measure of functioning.

  The result of this study suggested that the efficacy on the symptoms of ADHD in this group of partial responders is slightly lower than in the pivotal studies, which is expected. However no efficacy on functional measures was demonstrated.

- Study 314 was designed to assess morning vs. evening administration of guanfacine (1, 2, 3, and 4mg/day) in children aged 6-12 years with a diagnosis of ADHD. Results showed a statistically significant improvement following in both morning and evening administration and no difference between the 2 times of administration. The effect on the ADHD-RS-IV was 9.6 points with a 95% CI: (12.5, 6.7).

  Results on the functioning scale (the WFIRS-P) showed significantly greater improvement in the guanfacine arms compared to placebo for both morning and evening administration on the WFIRS-P Global score (change from baseline in placebo arm 0.20 (0.39) and in combined active arms (morning and evening) 0.36 (0.45); the difference was 0.16 (0.07, 0.25)) and in domain subscale scores for Family, Learning and School, Academic Performance, Behaviour in School, Social score, and Risk score.

  The results of this study suggest that the efficacy on the symptoms of ADHD is not dependant on time of administration (morning or evening). In addition, this study provides some support regarding efficacy on functioning. Only children (6-12) were included and hence the results do not contribute to resolving the doubts regarding efficacy in adolescents.

- Studies 303 and 305 were long-term open-label extension studies of Studies 301 and 304/205, respectively, in which long-term efficacy of up to 2 years was assessed. Maximum dose was 4mg/day.

  A total of 240 subjects (6-17) were enrolled and included in the Safety Population of study 303 and 42 subjects completed the study. A total of 262 subjects were enrolled in study 305 and 60 subjects completed the study. Although retainment in treatment over time (~20% at 2 years) raised some, uncertainties the results suggested that efficacy is maintained in the long-term in those patients who continue treatment.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: A phase 3, double-blind, placebo-controlled, multicentre, randomized-withdrawal, long-term maintenance of efficacy and safety study of extended-release guanfacine hydrochloride in children and adolescents aged 6-17 with Attention-deficit/Hyperactivity disorder			
Study identifier	SPD503-315		
Design	Phase 3, double-blind, placebo-controlled, randomized-withdrawal, multicenter		
	Open-label phase Duration of dose optimization period: Duration of dose maintenance period: Double-blinded randomized-withdrawal phase (optimal dose of SPD503 or matching placebo)		7 weeks 6 weeks
	Duration of maintenance period: Duration of dose-taper period:		26 weeks 2 weeks
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo, 15 weeks, 157 subjects
	SPD503		1-4 mg/day SPD503 for children aged 6-12 years, 1-7 mg/day SPD503 for adolescents aged 13-17 years; 15 weeks, 157 subjects
Endpoints and definitions	Primary endpoint	Treatment failure	Treatment failure defined as all subjects who met the following 2 treatment failure criteria at 2 consecutive study visits: During the double-blind randomized-withdrawal phase and compared with respective scores obtained at the double-blind baseline visit (Week 13/Visit 13), the treatment failure criteria are 1. ≥50% increase (worsening) in ADHD-RS-IV total score 2. ≥2-point increase in CGI-S score 3. Subject discontinued treatment for any reason
	Key secondary endpoint	Time to treatment failure	
Database lock	08 July 2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Randomized full analysis set (FAS), defined as all subjects who were randomized and received at least 1 dose of investigational product during the double-blind randomized-withdrawal phase Week 13 (Visit 13) to Week 39 (Visit 23)		
Descriptive statistics and estimate variability	Treatment	Placebo	SPD503
	Number of subjects	151	150
	Failed treatment Number (%) of subjects	98 (64.9)	74 (49.3)
	95% CI for percentage of treatment failures	57.3, 72.5	41.3, 57.3
Effect estimate per comparison	Difference in treatment failures from placebo		-15.6
	95% CI		-26.6, -4.5
	p-value		0.006

Notes	The primary efficacy analysis was performed on the treatment failure rates during the double-blind randomized-withdrawal phase for the randomized FAS. Percentages are based on the number of subjects in each treatment group. The overall treatment failure rates are the cumulative treatment failure rates at Week 36/Visit 23. The p-value is based on Cochran-Mantel-Haenszel statistic comparing the treatment groups with age group (6-12 and 13-17 years) and country as stratification factors and evaluated at 0.05 significance.		
Analysis description	**Key secondary analysis**		
Analysis population and time point description	Randomized FAS Week 13 (Visit 13) to Week 39 (Visit 23)		
Descriptive statistics and estimate variability	Treatment	Placebo	SPD503
	Number of subjects	151	150
	Median time to treatment failure (days)	56	218
	95% CI	44, 97	118, Non calculable
	p-value from log rank test	0.003	
Notes	For all randomized subjects time to treatment failure was analyzed using a logrank test stratified by age group and country.		

Title: A Phase 3, Randomised, Double-blind, Multicentre, Parallel-group, Placebo- and Active-reference, Dose-optimisation Efficacy and Safety Study of Extended-release Guanfacine Hydrochloride in Children and Adolescents Aged 6-17 Years With Attention-Deficit/Hyperactivity Disorder			
Study identifier	SPD503-316		
Design	A Phase 3, randomized, double-blind, multicenter, parallel-group, placebo-controlled, dose-optimization, efficacy and safety study, which included an active reference arm (STRATTERA)		
	Duration of main phase:		Dose-optimization Period: 4 weeks for children aged 6-12 years and 7 weeks for adolescents aged 13-17 years. Dose-maintenance Period: 6 weeks at optimal dose. Dose Taper: 2 weeks.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority		
Treatments groups	SPD503		1-4mg/day for children aged 6-12 years, 1-7mg/day for adolescents aged 13-17 years; 10-13 weeks double-blind treatment; 115 randomized subjects
	STRATTERA		0.5-1.4mg/kg/day for subjects <70kg at baseline, 40-100mg/day for subjects ≥70kg at baseline; 10-13 weeks double-blind treatment; 112 randomized subjects
	Placebo		Maximum 4-7mg/day; 10-13 weeks double-blind treatment; 111 randomized subjects
Endpoints and definitions	Primary endpoint	ADHD-RS-IV	Change from Baseline for the Attention-deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) total score at Visit 15 (Week 10 children aged 6-12 years and Week 13 adolescents aged 13-17 years) using last observation carried forward (LOCF)
	Key Secondary endpoint	CGI-I	Improvement in Clinical Global Impression-Improvement (CGI-I) analyzed by country and age group at Visit 15

	Key Secondary endpoint	WFIRS-P	Change from Baseline in Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) for the Learning and School and Family Domains at Visit 15 (LOCF)
Database lock	04 June 2013		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS) Baseline Visit (Visit 2/Week 0) to Visit 15 (Week 10/13)			
Descriptive statistics and estimate variability	Treatment group	Placebo	SPD503	STRATTERA
	Number of subjects	111	114	112
	Change from baseline mean	-15.0	-23.9	-18.6
	Standard deviation	13.1	12.4	11.9
Effect estimate per comparison	ANCOVA analysis of LS mean change from baseline	Comparison groups	SPD503 compared with placebo	STRATTERA compared with placebo
		Difference in LS means	-8.9	-3.8
		95% CI	-11.9, -5.8	-6.8, -0.7
		Effect size	0.76	0.32
		P-value	<0.001	0.017
Notes	LS mean and standard error, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group, age group, and country as fixed effects, and baseline value as a covariate.			
Analysis description	**Key Secondary analysis**			
Analysis population and time point description	Full Analysis Set (FAS) Visit 15 (Week 10/13)			
Descriptive statistics and estimate variability	Treatment group	Placebo	SPD503	STRATTERA
	Number of subjects	111	112	112
	Improvement in CGI-I at Visit 15	44.1%	67.9%	56.3%
	95% CI	34.9, 53.4	59.2, 76.5	47.1, 65.4
Effect estimate per comparison	Cochran-Mantel-Haenszel analysis	Comparison groups	SPD503 compared with placebo	STRATTERA compared with placebo
		Difference in % improved	23.7	12.1
		95% CI	11.1, 36.4	-0.9, 25.1
		P-value	<0.001	0.024
Notes	Improvement includes CGI-I categories ‘very much improved’ and ‘much improved.’ No improvement includes all other categories. P-value is based on Cochran-Mantel-Haenszel statistic comparing the respective treatment group to placebo with country and age group included as stratification factors.			
Analysis description	**Key Secondary analysis**			
Analysis population and time point description	Full Analysis Set (FAS) Baseline Visit (Visit 2/Week 0) to Visit 15 (Week 10/13)			

Descriptive statistics and estimate variability	Treatment group	Placebo	SPD503	STRATTERA
	Number of subjects	100	103	100
	Mean change from baseline at Visit 15 in WFIRS-P Learning and School Domain Scores	-0.378	-0.610	-0.571
	Standard deviation	0.5489	0.6695	0.6367
Effect estimate per comparison	ANCOVA analysis of LS mean change from baseline	Comparison groups	SPD503 compared with placebo	STRATTERA compared with placebo
		Difference in LS means	-0.22	-0.16
		95% CI	-0.36, -0.08	-0.31, -0.02
		Effect size	0.42	0.32
		P-value	0.0030	0.026
Notes	LS mean and standard error, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group, age group, and country as a fixed effect, and baseline value as a covariate.			
Analysis description	**Key Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	Placebo	SPD503	STRATTERA
	Number of subjects	106	109	105
	Mean change from baseline at Visit 15 in WFIRS-P Family Domain Scores	-0.387	-0.596	-0.507
	Standard deviation	0.6091	0.7706	0.6893
Effect estimate per comparison	ANCOVA analysis of LS mean change from baseline	Comparison groups	SPD503 compared with placebo	STRATTERA compared with placebo
		Difference in LS means	-0.21	-0.09
		95% CI	-0.36, -0.06	-0.24, 0.06
		Effect size	0.38	0.16
		P-value	0.006	0.242
Notes	LS mean and standard error, effect size, and p-value were based on type III sum of squares from an ANCOVA model for the change from Baseline (Visit 2/Week 0), including treatment group, age group, and country as a fixed effect, and baseline value as a covariate.			

Title: A phase 3, double-blind, randomized, multi-center, placebo-controlled, dose-optimization study evaluating the safety, efficacy, and tolerability of once-daily dosing with extended-release guanfacine hydrochloride in adolescents aged 13-17 years diagnosed With Attention-deficit/Hyperactivity disorder (ADHD)	
Study identifier	SPD503-312
Design	Phase 3, double-blind, placebo-controlled, randomized, multicenter; subjects were stratified by weight group and randomized 1:1 to treatment or placebo.
	A subject's optimal dose was a tolerated dose at which a ≥30% reduction from baseline in ADHD-RS-IV score was reached and a CGI-I score of 1 or 2.
	Duration of dose optimization period: 7 weeks at 1 to 7 mg/day

	Duration of dose maintenance period: Duration of dose tapering period:		6 weeks at optimal dose 2 weeks
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo, 15 weeks, 157 subjects
	SPD503		SPD503 up to 7 mg/day, 15 weeks, 157 subjects
Endpoints and definitions	Primary endpoint	ADHD-RS-IV	Change in the ADHD – rating scale-IV total score from baseline (Visit 2) to Week 13
	Key secondary	CGI-S	The clinical global impressions – severity (CGI-S) score
	Key secondary	WFIRS-P	The learning and school domain and family domain of The Weiss Functional Impairment Rating Scale – Parent Report (WFIRS-P)
Database lock	20 June 2013		

Results and Analysis

Analysis description	**Primary analysis**		
Analysis population and time point description	Full analysis set (FAS) defined as all subjects who were administered at least 1 dose of investigational product during the study Baseline visit (Visit 2/Week 0) to Week 13 (Visit 13)		
Descriptive statistics and estimate variability	Treatment	Placebo	SPD503
	Number of subjects	155	157
	Primary endpoint: Change from baseline mean	-19.5	-25.7
	Standard deviation	12.63	10.09
	Change from baseline LS mean	-18.527	-24.552
Effect estimate per comparison	Mixed model repeated measures (MMRM) analysis	Comparison groups	SPD503 compared with placebo
		Difference in LS means	-6.2
		95% CI	-8.7, -3.7
		Effect size	0.52
		P-value	<0.001
Notes	LS Mean, standard error, effect size, and p-value are based on repeated measures analysis for the change from baseline scores at Visits 3 to 13 (Weeks 1-13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (11 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including baseline and baseline-by-time as covariates. A negative difference in LS Mean (SPD503 - placebo) indicates a positive effect of active treatment over placebo.		
Analysis description	**Key secondary analysis**		
Analysis population and time point description	FAS Last on-treatment assessment (LOTA) is the last valid assessment obtained after baseline while on investigational product and before first dose taper.		
Descriptive statistics and estimate variability	Treatment	Placebo	SPD503
	Number of subjects	155	154
	Key secondary endpoint: CGI-S value at the LOTA		
	Number of subjects (%)		
	Normal/borderline mentally ill	56 (36.1)	78 (50.6)
	Mildly ill or greater	99 (63.9)	76 (49.4)
	p-value		0.010
Notes	The p-value is based on Cochran-Mantel-Haenszel statistic comparing the treatment groups with weight included as a stratification factor.		
Analysis description	**Key secondary analysis**		
Analysis population and time point description	FAS Baseline visit (Visit 2) to Week 13 (Visit 13)		

Descriptive statistics and estimate variability	Treatment	Placebo	SPD503
	Number of subjects	101	97
	Key secondary endpoint: Mean change from baseline to Week 13 in WFIRS-P Learning and School Domain Scores	-0.448	-0.565
	Standard deviation	0.6107	0.6784
	Change from baseline LS mean	-0.46	-0.57
Effect estimate per comparison	Mixed model repeated measures (MMRM) analysis	Comparison groups	SPD503 compared with placebo
		Difference in LS means	-0.12
		95% CI	-0.25, 0.02
		Effect size	0.22
		P-value	0.104
Notes	LS Mean, standard error, effect size and p-value are based on repeated measures analysis for the change from baseline scores at Visits 9, 11, and 13 (Weeks 7, 9, and 13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (3 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including baseline and baseline-by-time as covariates		
Analysis description	**Key secondary analysis**		
Analysis population and time point description	FAS Baseline visit (Visit 2) to Week 13 (Visit 13)		
Descriptive statistics and estimate variability	Treatment	Placebo	SPD503
	Number of subjects	101	105
	Key secondary endpoint: Mean change from baseline to Week 13 in WFIRS-P Family Domain Scores	-0.342	-0.415
	Standard deviation	0.5780	0.6029
	Change from baseline LS mean	-0.31	-0.37
Effect estimate per comparison	Mixed model repeated measures (MMRM) analysis	Comparison groups	SPD503 compared with placebo
		Difference in LS means	-0.06
		95% CI	-0.19, 0.08
		Effect size	0.11
		P-value	0.408
Notes	LS Mean, standard error, effect size, and p-value are based on repeated measures analysis for the change from baseline scores at Week 13 (Visit 13), with an unstructured covariance structure, random subject effect, treatment (2 levels), time (3 levels), treatment group-by-time, and weight group (4 levels) as fixed effects and including baseline and baseline-by-time as covariates.		

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Five pivotal studies as well as 5 supportive studies provided evidence regarding efficacy in this dossier. The pivotal studies include 4 short term studies of which 2 were dose response studies (with dose groups of 1/2/3/ and 4 mg/day and lasting 5/6 weeks) and 2 flexible dose studies (with doses 1-7mg/day and lasting 13 weeks). In addition a randomised withdrawal study was conducted which included a 26 weeks randomised withdrawal phase and with flexible dosing ranging between 1-7mg/day. All pivotal studies were randomised, double blind, and placebo controlled. One of the short-term studies included, in

addition to placebo, an active control arm: Atomoxetine. All included children and adolescents (6-17; one study (312) included only adolescents) with a diagnosis of ADHD according to DSM-IV.

Primary efficacy in all studies was the ADHD-RS-IV, which measures clinical symptoms of ADHD. This scale is established and validated for the purpose of measuring severity of ADHD symptomatology. In addition, 3 out of the 5 pivotal studies included a functional scale (the WFIRS) that monitors functional improvement following treatment, in addition to the monitoring of symptomatic improvement. The diagnosis of ADHD includes not only the symptoms of inattention and hyperactivity/impulsivity but also requires that these symptoms are accompanied by and are causing impairment in school performance and social functioning. Therefore it is expected that successful treatment will address not only symptomatic improvement but also alleviate impairment in functioning. Such improvement needs to be demonstrated in clinical trials for ADHD medication[1].

A GCP compliance finding in study 315 (the randomised withdrawal study) led to the exclusion of 23 subjects from = the efficacy analysis. The company notified all Competent Authorities and Ethics Committees in those Member States where the study was on-going of this serious breach of GCP =

A routine GCP inspection of study 316 revealed GCP issues in a site of this study. As a result, post hoc sensitivity analyses were performed to exclude this site from the primary and key secondary efficacy variables, and summaries of treatment-emergent adverse events. The results, inference, and conclusions from each of these analyses with the Site excluded are similar to those with the entire analysis set included in the analysis and hence none of these changes affect the overall study conclusions.

Efficacy data and additional analyses

All pivotal studies showed statistically significant results in favour of guanfacine against placebo on the primary endpoint, the ADHD-RS-IV symptoms scale, with mean effect sizes 0.5 and % responders higher than placebo by 13%-24% (21-22% in the flexible dose studies).

In addition, the effect of Guanfacine on this scale was numerically higher than for atomoxetine, even though the study was not powered to test superiority over atomoxetine. Specifically, the mean difference between placebo and Intuniv on the ADHD-RS-IV varied between 6.5 points (95% CI: 2.5 – 10.5) and 10.1 points (95% CI: 6.0 – 14.2) compared to a mean difference between placebo and atomoxetine of 3.6 (95% CI: 0.3 - 6.9). The proportion of responders in the active arms vs. placebo across the studies was higher by 13%-24% for guanfacine and by 13.1% for atomoxetine.

In the fixed dose studies there was a trend for a dose-response relationship, with the 4 mg dose providing better response compared to the lower doses. The exception was the relatively high response in the 1 mg dose compared to the 2 and 3 mg dose in study 304. This may be due to the fact that this dose group was restricted to patients weighing <110lb, hence mainly children (6-12) were included, suggesting that dose/kg was relatively high for this group.

The randomised withdrawal study also provides statistically significant support for efficacy on the ADHD symptoms scale with 16% (5% ; 27%) less relapses in patients who continued treatment on guanfacine compared to those who were switched to placebo.

Major concerns regarding the efficacy of guanfacine were raised during the assessment. These included the lack of efficacy in adolescents, the possibility of symptoms correction being predominantly due to sedation rather than a direct symptomatic effect, and the lack of effect on functioning. These concerns were however addressed satisfactorily during the procedure as explained below.

[1] Guideline on the clinical investigation of medicinal products for the treatment of attention deficit hyperactivity disorder (ADHD); EMEA/CHMP/EWP/431734/2008 Committee for Medicinal Products for Human use (CHMP).

The concern regarding lack of efficacy in adolescents compared to children between the age of 6 and 12 was eventually resolved as the company was able to provide a variety of plausible reasons for failure to show efficacy in adolescents, which included: too low doses in the fixed dose studies, small samples, and high placebo response in studies 316 and 315. In addition, efficacy was demonstrated in the specifically designed adolescents study (study312). In addition the applicant provided data on long-term efficacy in adolescents generated in the ongoing open label study SPD503-318. The mean change from baseline after months 6, 12 and 18 on the ADHD-RS-IV total score was comparable between the children and adolescents groups, despite the fact that baseline scores in the children were higher. The proportions of adolescents who were rated as normal to borderline mentally ill at 6, 12 and 18 months were respectively 72.2%, 76,3% and 87,0% and were higher than the proportions in the children groups for the respective times. This is not surprising, since a similar effect with a different baseline score is expected to lead to a higher proportion of adolescents falling into the category “normal or borderline mentally ill” as compared to children. These preliminary long term data provided some reassurance that a sustained effect of INTUNIV on ADHD could be expected in adolescents and that this may translate into a reasonable proportion of subjects being defined as “normal or borderline mentally ill”. However, the lack of a placebo control arm restricts the validity of these results.

The question whether efficacy may in fact be due only to the sedating effect of guanfacine rather than a direct effect of guanfacine on the core symptoms of ADHD was carefully discussed. In support of the sedation-efficacy hypothesis is the fact that sedation was a common AE in the short term studies (49% in guanfacine vs. 28% in placebo) and that these events led to study discontinuation in almost 12% of all guanfacine-treated patients, suggesting that these symptoms were severe. Furthermore, study results showed that efficacy among patients with inattentive subtype ADHD is consistently lower than efficacy among patients with combined subtype ADHD, suggesting that sedation may be an important element in influencing efficacy through reduction of hyperactivity. This was not due to the smaller numbers in the inattentive subtype but to a smaller effect size, in turn suggesting that sedative effects – also frequently reported as adverse events - may contribute to the effect of Guanfacine.

On the other hand, effects on the inattentive subscale of the ADHD-RS-IV were in the same order of magnitude as effects on the hyperactive subscale, which is not supportive of the sedation hypothesis (although this may be due to sedation lowering hyperactivity, which in turn allows for improvement in attention). The Applicant also provided analyses stratified for patients who did and who did not report sedation as an AE (for fixed dose studies 301 and 304 and flexible dose studies 312 and 316). The additional data show that efficacy on ADHD symptoms have been observed also in subjects without reported sedation. Additional data also show no clear temporal relationship between efficacy and reporting of sedation as an AE. These results suggested that efficacy may be achieved at least partially via a different mechanism of action than that of involved in sedation. However, the contribution of sedation to the reduction on the symptom scale could not be completely excluded.

The uncertainties raised during the procedure with respect to the questionable effect of guanfacine on functioning, also in connection with the mechanism of action of guanfacine which causes sedation and the nature of the disease were also discussed by the CHMP . Only one instrument used in this dossier, the WFIRS, addressed directly functioning and the results with respect to this instrument are inconsistent since out of the three studies in which this measure was used (studies 312, 316, and 315) only one showed significant results (study 316). The argument by the company, that effect on functioning was not demonstrated for atomoxetine in study 316, was noted by the CHMP. The company argued also that the WFIRS may not be a sensitive measure, which was also supported by the absence of a significant effect for atomoxetine in study 316. The CHMP considered that WFIRS may indeed be an insensitive and unreliable measure, not only across studies, but also with time as suggested by the fact that the effect seemed stronger in weeks 7 and 9 of study 312 than at study end (week 13). However, while lack of

sensitivity of the WFIRS may explain the failure to show an effect on functioning, the lack of evidence for such effect remains. The additional analyses provided in subgroups with and without sedative AEs could not provide data to conclude and resolve this uncertainty. The company further argued that in assessing the effect of guanfacine on functioning, not only WFIRS should be taken into account but also CGI and CPRS/CTRS. However, the CPRS/CTRS (Conner's Parent/teacher Rating Scale) is a rating scale designed to evaluate DSM-IV ADHD symptoms but not functioning. With respect to CGI, this was not considered as an optimal suitable measure in this case as this is a global measure of the patients' condition that may be influenced by either symptoms, functioning or both. Therefore, improvement on this scale may equally reflect improvement on symptoms and/or improvement in functioning and it is not possible to disentangle the two and hence to ascertain whether an effect on this measure is indeed reflecting an effect on functioning.

The CHMP considered that although there were methodological weaknesses in the way functioning had been assessed in the studies and that functioning had been inconsistently shown, failure of some studies with guanfacine to prove a clinically significant improvement had to be interpreted with caution. This concurred as well with the input from the SAG psychiatry experts who highlighted in particular the methodological difficulties pertinent to the measurement of functioning in psychiatric disorders and in ADHD in particular, and that symptomatic improvement might be considered as a first step towards recovery and therefore as a clinical significant improvement in itself.

Additional expert consultation

In the course of the evaluation procedure, the CHMP identified the need for expert input and thus psychiatry SAG meeting was convened including also patient representatives. The parents of two ADHD patients and a young adult affected by ADHD participated in this meeting as well as expert physicians.

The positions of the group on the following questions are summarized below:

Question 1

Bearing in mind that no improvements were observed in functioning in school/family, the SAG is asked to discuss the clinical relevance of the efficacy of Intuniv on symptoms only, also taking into consideration that it may be the result of sedation rather than a true effect on the core symptoms of ADHD.

The SAG acknowledged that ADHD treatment is multifaceted and that the reduction of symptoms is to be considered as a first step in the management of the disorder. In psychiatric disorders in general, symptom reduction is of importance to minimize burden of the disorder and to enable the patient to recover in his/her functioning level. Therefore, the observed efficacy on symptoms of ADHD, even though seemingly modest, has been considered by the SAG as clinically relevant in itself.

In light of the methodological difficulties pertinent to the measurement of functioning in psychiatric disorders and in ADHD in particular, the failure of some studies with guanfacine to prove a clinically significant improvement has to be interpreted with caution. This is due the lack of both evaluated and comprehensive assessments of functioning in psychiatric disorders. Given the fact that the ICF of the WHO, which shall describe function levels, has a high variety domains, which mix symptoms and impairment/functioning, this issue remains unresolved for clinical trials in children and adolescents with psychiatric disorders. Methodological assessment of function in psychiatric disorders is a complex and yet unresolved issue. Therefore, a failure in WFRIS cannot be interpreted as a failure of improvement of functioning in general. There are indeed different types of impairment and disabilities and none of them can be considered as a satisfactory measure of the effect of a drug on the functioning of these patients.

Social impairment for example is a function of the child but also of his/her environment (e.g. safe environment, parenting style, tolerance of the environment for the disorder).

There is some evidence to support that sedation is mostly prevalent at the start of the treatment and that guanfacine may work on some ADHD domains outside its sedative effects. For example, the lack of temporal relationship observed in the trials between the sedation SAEs and the effects on core symptoms of ADHD would not be consistent with a simple sedative effect of the medication.

With regard to sedation, the group considered that this is a very significant AE which appears not to be well defined especially in the case of ADHD, where symptomatic improvement and sedation are difficult to disentangle. Patient representatives expressed also serious concerns over the reported risk of sedation. In particular, evening sedation may not be acceptable for some patients and their families as evening is a time for family life and after school activities (see also question 2). On the other hand, sedation may be beneficial for some patients with sleep problems, as from the clinical perspective, sedation may help in some cases to manage symptoms such as agitation

Question 2

The SAG is asked to discuss the implications of the observed safety concerns in terms of the risk of bradycardia, hypotension, somnolence, sedation, syncope, accidents and increases in BMI of Intuniv in its clinical (long term) use. The SAG should also discuss the feasibility of measures intended to minimize those safety concerns.

Overall, the SAG pointed out that safety is of concern with this medicinal product and that caution should apply as for every medication intended for children. This is especially true if a clinical trial detect any signals for specific assessments to assure patients safety (e.g. QT prolongation).

Sedation/Somnolence

Sedation is of significant concern and appears not to be well defined especially in case of ADHD (See Q1). Patient representatives and physicians were concerned about the implications in terms of cognitive impairment and neurocognitive development when using a sedative drug in children.

In light of the results of the trials, sedation should be closely monitored during the first few weeks of treatment with guanfacine and parents/patients should be informed about the risk of both sedation and somnolence. Gradual adjustment of the dose should also be recommended to try and minimise this AE.Sedation may also lead to accidents. The related risks of accident (e.g. bicycle, car) were also of significant concern for patient representatives as for physicians and the SAG considered that this should be further assessed by the applicant in a prospective manner. This is especially of importance for adolescents who may be active participants in traffic as car drivers etc. A recent study (Dalsgaard S et al., The Lancet, Feb 2015) has shown that patients with ADHD have higher than expected mortality rates (5.8 vs 2.21) and that 68.4% of deaths were due to unnatural causes (homicide, suicide, accident, or undetermined**)** of which 77.8% were due to accidents.To date, there is no data assessing executive functioning of ADHD patients treated with guanfacine vs. ADHD patients not treated or treated with approved medication.

Therefore, specific warnings in the labelling as well as a comprehensive post marketing programme would be needed to better characterise this serious AEs (e.g. specific questionnaires, neuropsychological testing to differentiate between symptom reduction and true sedation) and to provide adequate risk minimisation measures.

Overall, the group felt that sedation was not very clearly described and should be further investigated and controlled.

Cardiovascular effects

Cardiovascular effects are also of serious concern and increase in the QTc in particular.

Blood pressure and heart rate should be measured at the start of the treatment and periodically during the course of the treatment.

With regard to QTc increase, it should be mandatory to assess a detailed cardiovascular history both at personal and family level (e.g. sudden deaths, syncope). This detailed medical history together with a comprehensive paediatric examination would then allow physicians to apply clinical judgement whether or not an ECG should be performed and at which frequency. Some of the SAG experts would even advocate, that in addition to the family being asked about sudden death/syncope, all patients have a pre-treatment ECG and at a time when steady state levels are achieved in the clinical long term prescription, or when the patient develops any cardiac or related-neurological symptoms.

Label warnings are also advised with respect to interaction with other drugs known to increase the QT (about 20% children with ADHD are treated also with second generation antipsychotics that could impact on QTc prolongation).

BMI

There is a signal that guanfacine may increase the BMI, even more in patients who have already a BMI at the border to obesity. This is of concern as ADHD is associated with obesity and therefore the product may increase this risk further.

Once weight is put on, it may be difficult to lose. With respect to weight gain, the SAG was therefore of the opinion that patients on guanfacine need to have their BMI and metabolic parameters (cholesterol, glucose, triglycerides) assessed before the start of the treatment and at least annually in the long term use, or sooner if there any significant symptoms related to weight gain or any sudden increase in weight. Diet advice is needed as well to minimise this risk.

Further data using the corrected BMI (for age and gender) are needed to better estimate this AE. The relationship between weight gain and sedation should also be further investigated.

Question 3

The SAG is asked to discuss whether there is a subset of patients within the scope of the applicant's proposed indication that would benefit the most from treatment by Intuniv e.g. patients with ADHD who have problems with insomnia, sleep or appetite disturbances or suicidal thoughts as well as in the case of insufficiently effective and/or intolerance for typical first line (i.e. methylphenidate and atomoxetine) treatment.

The SAG considered that there is no specific ADHD population that can be described in details or would benefit exclusively from guanfacine as first line treatment. In general, effect sizes of guanfacine seem to be moderate. Therefore, if a medication in children and adolescents with ADHD is indicated, treatment with stimulants has to be considered as fist line treatment due the high efficacy. However, the group agreed that although stimulants are considered, in therapeutic guidelines and in clinical practice, to be the first choice for pharmacological treatment for ADHD, the use of guanfacine should not necessarily be restricted to second or third line treatment. There may be cases indeed where stimulant would not be the most appropriate treatment due for example to specific clinical features of the patients (e.g. comorbidities such as tics, weight loss or insomnia) or clear contraindications of stimulants.

The group pointed out that it would be important to measure prescription rates if the drug is approved as they do not expect guanfacine to take a prominent place in the therapeutic arsenal.

Similar advice as to other ADHD drugs with respect to the validation of the diagnosis, the decision about treatment (together with the parents and the patients), and continuous treatment monitoring by a specialist (e.g. a child and adolescent psychiatrist) should be incorporated in SmPC.

Question 4

4. The SAG is asked to discuss the observed efficacy of Intuniv in adolescents as compared to children, and whether it could support the use of Intuniv in this population.

The SAG noted that less adolescents than children were studied in the clinical programme. Aside from study 312, studies were not powered to detect efficacy in the subgroup of adolescents. In study 312 an effect of guanfacine was shown on symptoms. With regard to the relevance of data on functioning, the group had the same views as for functioning assessment in children (see question 1).

The clinical presentation of ADHD in adolescents would be expected to shift from hyperactivity to inattention, which is well described in studies. Bearing this in mind, the group considered that efficacy in adolescents has been shown in the dedicated study 312. As higher doses were used in study 312, the SAG considered that an appropriate dosage seems to be relevant for effects. Therefore, further studies should be conducted to further define the appropriate dosage in adolescents. The SAG also underlined that in their opinion there would be no pharmacological or clinical rationale for stopping the medication at the age of 12.

During the oral explanation, patients representatives were invited to express their views on on the following aspects:

- As a patient / carer and your expectations with regard to ADHD medication how much do you feel Guanfacine would meet these expectations in terms of symptom relief and improvement in daily life? It would be good to hear your perspective on both of these aspects.

As a patient / carer what are your major concerns about the main risks that have been seen so far with the clinical use of guanfacine (i.e. sedation, weight gain and cardiovascular safety concerns). To what extent would the concerns in your view potentially limit its use by patients".

As a general principle, patients representatives are expecting from an ADHD medication to help children/adolescents to develop in a postive way, especially socially -wise and ultimately to have a better quality of life. They considered the effects on symptoms as a first step towards revovery. It was indeed acknowledged that symptom relief may help to improve the way the ADHD children/adolescent interacts with its environment, thereby improve their self-perception and give them a chance to move on towards recovery. Moreover patient representatives highlighted that, according to them, the second step should be an improvement on functioning at school, home and in the daily activities.

Sedation was perceived by the patient representatives as a very important safety issue. In particular they expressed concerns that sedation may stigmatise even further ADHD patients and thereby reinforce exclusion from their environnement, especially from their peers at school. Also concerns were raised about the risk that sedation may interfere with the afterschool family life and with any extra curriculum activities in general.

Last they would like to be reassured that despite the occurence of sedation, ADHD children/adolescent would be able to acquire properly all of the cognitive skills that are key to any child development. The CHMP welcomed the contribution of the patients and concurred in particular with their concerns about the potential consequences of sedation on the cognitive development of ADHD children and adolescents. In order to investigate the long term safety (especially effects on neurocognitive function) of Intuniv in

Children and Adolescents Aged 6- 17 Years with ADHD, the CHMP requested the MAH to conduct a post-authorisation safety study.

Overall, the consulted patient representatives could see a potential use of guanfacine for some patients but they were advocating for a close medical support and monitoring from their physician if they were to accept to give this drug to their children/adolescents.

SAG Experts highlighted also that, the clinical management of ADHD patients should be based on a multidisciplinary approach and this was duly reflected in the therapeutic indication by the CHMP.

2.5.3. Conclusions on the clinical efficacy

The clinical efficacy data submitted were considered satisfactory and supportive of the indication of guanfacine for the treatment of treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective.

Treatment with guanfacine resulted in an improvement in ADHD symptoms (on hyperactive symptoms and to a lesser extent on inattentive subtypes) in children and in adolescents. The results suggested that although contribution of sedation to the reduction on the symptom scale could not be completely excluded, efficacy of guanfacine may be achieved, at least partially, via a different mechanism of action. The effect on functioning was inconsistently shown, but, taking into account the methodological difficulties to show a functional improvement in ADHD and taking also into consideration experts' view, the symptomatic effect observed with guanfacine was considered by the CHMP as clinically meaningful.

Overall, the CHMP concluded that the available clinical data demonstrated an effect of guanfacine on the symptoms of ADHD.The CHMP stressed also that guanfacine, like other medicines authorised for the treatment of ADHD, must only be used as part of a comprehensive treatment programme, typically including psychological, educational and social measures. The CHMP acknowledged the differences in display of the information contained in the SmPC of Intuniv compared to the other ADHD medications which have been authorised so far at national level. In particular, the wording of the therapeutic indication for intuniv is focused on the targeted population and on the multidisciplinary approach of the clinical management.

2.6. Clinical safety

Similar to other α-2 adrenergic compounds such as clonidine, safety-profile of guanfacine is characterised by undesirable side-effects such as (orthostatic) hypotension, bradycardia, hypno-sedation, fatigue, and headache. These unwanted effects were shown to be very common and limit tolerability. After discontinuation, in particular after abrupt cessation of treatment, rebound hypertension and tachycardia may occur.

The responses of the applicant clarified methods of collection of safety-data. In particular comparison of the standard-ascertainment (i.e. single question to tap undesirable effects) versus the standardised questionnaire (SSEQ) tapping specific domains was outlined satisfactory. For some domains of adversity the SSEQ was shown to be more sensitive, for the most frequent adverse effect (somnolence, sedation and fatigue), sensitivity appears similar.

Patient exposure

The safety-population was defined as all subjects who used at least one dose. The applicant performed 17 studies in ADHD-patients 6-17 years (Prolonged-release-formulation: n=2411) and 14 studies in healthy

adult volunteers (Prolonged-release-formulation: n=486) as part of the development programme. Most studies used the Prolonged-release formulation, in 5 studies other formulations were used (n=156). In patients, up to 7 mg/day dose titration was used and up to 9 mg/day forced dose-escalation. One further safety study was conducted in paediatric patients with anxiety disorders. A further long-term (2 year) study is currently on going.

Of the total of 2411 exposed patients, 1718 were 6-12 years of age and 693 were 13-17 years old. Mean duration of exposure was 142 days, median exposure-time 70 days. A total of 336 patients were exposed 360 days or more, of which 101 were exposed more than 720 days. 1468 patients were exposed to the high dose levels (>0.09 mg/kg) with a mean duration of about 74 days, median 35 days.

For the long-term studies 643 patients were exposed for a mean duration of 242 days (median = 150 days). A total of 136 patients were treated 270-720 days and 66 for more than 720 days. A total of 382 patients were exposed to high dose-levels (>0.09 mg/kg) with a mean duration ≈ 160 days, median ≈ 85 days treatment duration.

In healthy volunteers, dose-by-weight exposures were not summarised. 296 subjects received a single 4 mg dose, the mean single dose was 3.2 mg.

Table 5. Numbers of exposed subjects

	Subjects exposed	High dose levels (>0.09 mg/kg)
Healthy volunteers	495	Unknown
All patients	2411	1468
Fixed dose	513	164
Randomized	1419	641
Long-term	643	382

In the long-term studies 9 patients aged 6-12 years old were exposed to guanfacine 1 mg for more than 90 days. 81 were exposed to 2 mg >90 days, 133 to 3 mg, and 113 were exposed to 4 mg or more for >90 days. A total of 84 patients 6-12 years old were exposed for 360 days or more, of whom 58 were exposed to 3 or 4 mg.

For patients 13-17 years of age these numbers were: 1 patient exposed to 1 mg for >90 days, 18 patients to 2 mg, 28 to 3 mg and 55 patients 13-17 years of age were exposed to 4 mg or more for more than 90 days. A total of 28 patients 13-17 years old were exposed for 360 days or more, of whom 24 to 3 or 4 mg.

In the long-term studies, duration of exposure to higher recommended dose-levels was very limited due to discontinuations, with a mean duration ≈ 74 days (median ≈ 35 days). To allow assessment of safety in the paediatric population, in particular assessment of 12-month exposure, a sufficient number of patients exposed to high recommended dose-levels is mandatory. According to ICH Topic E1 on Population Exposure (*The Extent of Population Exposure to Assess Clinical Safety*), the requirement is of 100 patients to be exposed for at least 1 year. The submitted data include safety results regarding 1 year exposure for only 84 patients 6-12 years old and 28 patients 13-17 years old. Only 82 patients (58 children and 24 adolescents) were exposed to 3 or 4 mg of guanfacine for more than one year. Therefore safety of long-term exposure to guanfacine, in particular to the higher doses, cannot be reliably assessed, while ADHD-treatment typically requires long-term treatment.

Regarding discontinuations, it is noted that in guanfacine-treated patients both discontinuations in general and discontinuations due to AE's were twice as frequent as compared to the active comparator

atomoxetine. Discontinuations due to AE's were more than six times the rate in placebo-treated patients, even higher for the 4 mg dose-group.

The Applicant justified the high (61.8%) withdrawal in the long-term studies with "difficulties and inconveniences associated with long-term study participation". Although that undoubtedly played a role, it may have been enhanced by unsatisfactory treatment results associated with guanfacine-tolerability, in particular due to somnolence and sedation.

Adverse events

In the overall pool, rates of treatment-emergent adverse events (TEAE's) were higher in guanfacine-treated patients as compared to placebo- or atomoxetine-treated patients, in particular regarding severe TEAE's (8.8% versus 1.7% (placebo)/ 1.8% (atomoxetine), TEAE's related to investigational product (73.2% versus 36.7% (placebo)/ 55.4% (atomoxetine), and TAE's leading to study discontinuation (10.8% versus 1.3% (placebo)/ 4.5% (atomoxetine)), see table below.

Table 6. rates of treatment-emergent adverse events (TEAE's) in the overall pool

	Placebo N=973			SPD503 N=2411			Strattera N=112		
	n	(%)	m	n	(%)	m	n	(%)	m
Any TEAE	620	(63.7)	1820	2046	(84.9)	10659	76	(67.9)	424
Serious TEAEs	8	(0.8)	10	49	(2.0)	66	0	(0.0)	0
Severe TEAEs	17	(1.7)	27	213	(8.8)	309	2	(1.8)	2
TEAEs Related to Investigational Product	357	(36.7)	740	1765	(73.2)	5958	62	(55.4)	278
TEAEs Leading to Study Discontinuation	13	(1.3)	22	261	(10.8)	325	5	(4.5)	5
TEAEs Leading to Death	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0

There were no meaningful differences by age-group for rates of TEAE's.

Regarding TEAE's occurring with a frequency of 5% or more in any treatment-group in the overall pool, frequencies for all TEAE's, and for total number of TEAE's classified as 'severe' were as shown in the table below:

Table 7. TEAE's occurring with a frequency of 5% or more in any treatment-group in the overall pool

Preferred term	Placebo (N=973) n	(%)	m	SPD503 (N=2411) n	(%)	m	Strattera (N=112) n	(%)	m
Somnolence	97	(10.0)	108	979	(40.6)	1589	20	(17.9)	32
Headache	159	(16.3)	220	660	(27.4)	1145	22	(19.6)	36
Fatigue	57	(5.9)	63	437	(18.1)	628	24	(21.4)	32
Abdominal pain upper	47	(4.8)	51	289	(12.0)	377	2	(1.8)	3
Sedation	19	(2.0)	25	245	(10.2)	323	2	(1.8)	2
Dizziness	48	(4.9)	51	222	(9.2)	279	17	(15.2)	24
Upper respiratory tract infection	58	(6.0)	61	195	(8.1)	247	2	(1.8)	2
Irritability	34	(3.5)	35	183	(7.6)	217	4	(3.6)	4
Nausea	52	(5.3)	60	182	(7.5)	215	30	(26.8)	54
Decreased appetite	52	(5.3)	66	175	(7.3)	198	31	(27.7)	44
Nasopharyngitis	46	(4.7)	50	164	(6.8)	216	3	(2.7)	3
Insomnia	37	(3.8)	38	155	(6.4)	186	8	(7.1)	10
Vomiting	43	(4.4)	49	144	(6.0)	166	18	(16.1)	29
Diarrhoea	46	(4.7)	54	130	(5.4)	168	2	(1.8)	3
Pyrexia	25	(2.6)	25	127	(5.3)	147	3	(2.7)	4
Cough	39	(4.0)	42	121	(5.0)	141	4	(3.6)	4
Abdominal pain	31	(3.2)	46	89	(3.7)	119	19	(17.0)	31
Anxiety	12	(1.2)	19	42	(1.7)	51	7	(6.3)	18
Nervousness	9	(0.9)	11	17	(0.7)	20	6	(5.4)	6
Subjects with at least one TEAE	620	(63.7)		2046	(84.9)		76	(67.9)	
Mild	340	(34.9)		722	(29.9)		46	(41.1)	
Moderate	263	(27.0)		1111	(46.1)		28	(25.0)	
Severe	17	(1.7)		213	(8.8)		2	(1.8)	

The TEAE that was most frequently considered by the investigator to be related to the investigational product was somnolence (guanfacine: 39.4%; placebo: 9.7%; atomoxetine: 16.1%). Sedation was also frequently considered to be related to treatment (guanfacine: 10.0%; placebo: 1.8%; atomoxetine: 1.8%).

Regarding the most frequent TEAE of somnolence, a dose-response relationship was observed in the randomized pool. A dose-response relationship was also observed for the TEAE 'sedation' and for 'dizziness'. TEAE frequencies did not markedly differ between age-groups.

In healthy (adult) volunteers, headache was reported by 16.8% of guanfacine-treated subjects, somnolence by 12.0% and dizziness by 10.9%. All events were dose-proportionate.

Regarding TEAE's rated by investigators as 'severe', nervous system disorders were observed in 4.6% of patients treated with guanfacine (placebo: 0.5%; atomoxetine: 0.0%), primarily severe somnolence (2.7%; placebo: 0.1%; atomoxetine: 0.0%). Severe treatment-emergent psychiatric disorders were observed in 1.4% of guanfacine-treated patients (placebo: 0.2%; atomoxetine: 0.9%).

Premature discontinuations

TEAE's leading to study discontinuation occurred in 10.8% of guanfacine-treated patients (placebo: 1.3%; atomoxetine: 4.5%), in particular nervous system disorders (guanfacine: 5.4%; placebo: 0.4%; atomoxetine: 1.8%), especially somnolence (guanfacine: 2.5%; placebo: 0.0%; atomoxetine: 1.8%). For somnolence, treatment discontinuations were dose-proportionate with a maximum of 6.0% dropout due to somnolence in the 4 mg dose-group. A similar trend was observed for sedation, associated with 5.3% study-discontinuations in the 4 mg dose-group and hypotension associated with 1.3% dropout with 4 mg guanfacine. Treatment-emergent psychiatric disorders resulted in premature study discontinuation in 2.1% of guanfacine-treated patients (placebo: 0.2%; atomoxetine: 0.9%).

In the overall pool, premature discontinuations (irrespective of reason specified) occurred in a total of 44.3% of guanfacine-treated patients versus 32% of placebo-treated patients. Among patients treated using atomoxetine (n=112) 20.5% did not complete the study. In the long-term studies a total of 61.8% of enrolled patients dropped out. Discontinuations attributed to AE's occurred in 12.9% of patients enrolled in long-term studies.

A total of 11.8% of patients in the short-term studies discontinued study participation due to a sedative event.

Overall, psychiatric TEAE's occurred in 21.7% of guanfacine-treated patients (placebo: 11.9%; atomoxetine: 22.3%). Psychiatric TEAE's with highest incidences were irritability (6.3%; placebo: 2.8%; atomoxetine: 2.7%), affect lability (2.1%,; placebo: 1.3%; atomoxetine: 0.9%), anxiety (1.7%; placebo: 1.2%; atomoxetine: 6.3%), aggression (1.5%; placebo: 1.1%; atomoxetine: 1.8%), and depression (1.0%; placebo: 0.8%; atomoxetine: 2.7%). Suicidal ideation occurred in 0.5% of guanfacine-treated patients (placebo: 0.3%; atomoxetine: 0.0%). In 5 studies the Columbia-Suicide Severity Rating Scale was administered. Analyses of these assessments revealed no results that suggest a different risk of suicidal behaviour in guanfacine-treated patients as compared to placebo-treated patients.

Among the patients treated using guanfacine for anxiety disorder, safety profile was similar to the profile in ADHD-patients. A total of 8 guanfacine-treated patients (no placebo-treated patients) discontinued due to TEAEs. TEAE's leading to discontinuation with multiple occurrences were fatigue (n=2) and (postural) dizziness (n=3).

Serious adverse event / deaths / other significant events

There were no deaths in the clinical studies. In the overall pool, serious TEAE's were observed in 2.0% of guanfacine-treated patients (placebo: 0.8%; atomoxetine: 0.0%). Syncope occurred in 16 guanfacine-treated patients (0.7%; placebo: 0.2%; atomoxetine: 0.0%). All patients recovered with either unchanged dose or after withdrawal of guanfacine. In the long-term studies syncope occurred in 7

patients (1.1%). Among 441 healthy (adult) volunteers, 4 subjects reported SAE's including 2 syncope's. Among healthy volunteers enrolled in the QTc-study 5 subjects reported SAE's including 3 syncope's. Hypotension, including orthostatic hypotension, was reported in 5.7% of guanfacine-treated patients (placebo: 0.7%; atomoxetine: 0.9%), including 4 patients in whom hypotension was rated as 'severe' (none in the placebo and atomoxetine groups). Pallor was reported in 10 guanfacine-treated patients (0.4%), none in the placebo and atomoxetine groups.

As a reference regarding syncopes, at the optimisation visit, mean (sd) supine pulse of guanfacine-treated patients had dropped -6.5 (11.9) bpm (placebo: +0.8 (10.8); atomoxetine: +1.7 (11.6)) as compared to baseline. Mean supine systolic blood pressure had dropped -3.5 (9.6) mmHg (placebo: -0.7 (8.0); atomoxetine +1.1 (7.6) mmHg) and mean diastolic blood pressure had dropped -3.0 (8.5) mmHg (placebo: -0.6 (7.6); atomoxetine: +2.6 (8.7) mmHg). Largest decreases in guanfacine-treated patients were pulse -75 bpm (standing pulse, optimisastion visit), systolic blood pressure -66 mmHg (seated, maintenance visit), diastolic blood pressure -61 mmHg (seated, maintenance visit).

Injury, poisoning and procedural complications

In the overall pool, injury, poisoning or procedural complications occurred in 10.4% of guanfacine-treated patients (placebo: 7.1%, atomoxetine: 1.8%). Contusion occurred in 1.7%, skin laceration in 1.4%, excoriation in 1.2%, joint sprain in 1.0%, sunburn in 0.8%, fall in 0.4%, and head injury in 0.4%.

The occurrence of hypotension in almost 6% of guanfacine-treated patients, and syncope in 16 patients (0.7%) is of serious concern. Syncope is a serious risk associated with falls, accidents and physical trauma in children and adolescents. In published literature, syncopes were also reported in patients receiving guanfacine-treatment for Tourette's syndrome (King et al, 2006). Similar to somnolence and sedation, low pulse and blood pressure and syncope may be associated with the anti-adrenergic mechanism of action of guanfacine. Syncope may be related to (postural) hypotension due to decreased vascular tone, or may be mediated via adrenergic CNS-pathways. Syncope may increase risk of falls and (traffic-) accidents. Regarding reported frequencies of injury, poisoning or procedural complications, it is noticed that the risk in atomoxetine-treated patients is low (1.8%) which may be associated with reduction of ADHD-symptoms, possibly lowering the risk of accidents towards the level observed in the general (child and adolescent) population. The risk in the placebo-group (7.1%) may in some degree reflect the level of risk associated with ADHD-symptomatology, which is higher as compared to the general population. The guanfacine-treatment associated risk (10.4%) is increased as compared to placebo. It is questioned whether guanfacine-induced somnolence and sedation may result in a net *increase* of risk of accidents, beyond the a priori increase associated with the underlying disease.

Rebound / withdrawal / dependence

No pre-clinical testing for abuse-potential was performed. There were 2 reports of abuse or misuse in the study programme and 5 reports from post-marketing surveillance. As part of the program, abrupt cessation of treatment was studied as compared to dose-tapering in healthy adult volunteers. That study revealed slightly higher increase in (systolic) blood pressure after abrupt cessation (14/6 mmHg) as compared to tapering (9/8 mm) and more TEAE's in that group, in particular more dry mouth, nose congestion, fatigue, dizziness, headache and pharyngeal pain.

In paediatric ADHD-studies post-dose increases up to 10 mmHg systolic blood pressure were observed. In a long-term randomised withdrawal study a small guanfacine-cessation associated blood pressure increase was shown of 3.2 (±8.69) mmHg systolic and 1.2(±8.56) mmHg diastolic blood pressure.

A diagnosis of ADHD is known to increase risk of substance abuse irrespective of treatment. Regarding the psychotropic effects of guanfacine, in particular the hypno-sedative effects, this product may be prone to

abuse including overuse, divergence and dependence in this a priori susceptible target population. This risk is confirmed by the listed reports of abuse or misuse. No pre-clinical or clinical testing of abuse-potential has been performed. Rebound effects other than cardiovascular effects were not evaluated. Use of guanfacine in the vulnerable paediatric ADHD population, outside the controlled environment of the study-programme, may include a higher risk of abuse as compared to this risk in the study programme. However, the applicant provided adequate justifications to support low abuse potential for guanfacine.

Central nervous system: cognitive effects

A randomized, double-blind, multi-center, placebo-controlled, dose-optimization study (n=182) was performed to assess the effect of guanfacine on cognitive function, safety, tolerability, and efficacy of guanfacine 1- 3mg in children and adolescents aged 6-17 years diagnosed with ADHD (study 206). Effects of 6.5 weeks treatment were studied using the Cambridge Neuropsychological Test Automated Battery (CANTAB) Choice Reaction Time (CRT) test 2, 5, and 8 hours post-dose (primary endpoint), the Digit Symbol Substitution Task/Coding Test (DSST/Coding), and the Spatial Working Memory (SWM). Also the Permanent Product Measure of Performance (PERMP) math test was administered at several hours post-dose. There were no meaningful differences as compared to placebo in (subscales of) tests or subgroups of patients. PERMP results showed significant improvement in the guanfacine-group as compared to placebo, especially in patients 6-12 years of age. The primary efficacy-outcome in this study (ADHD-RS-IV) showed statistically significant improvement of ADHD-symptoms in 6-12 year old, but not in patients 13-17 years old. In this study, somnolence was reported in 41.3% of all patients treated using guanfacine (placebo: 22.8%). Sedation was reported in 7.4% (placebo: 5.3%), and both fatigue and irritability in 5.0% (placebo: 0%, 0%). Overall sedative events were reported in 48.8% of patients treated with guanfacine and 28.1% of patients treated with placebo. As a part of the safety assessment, the Pictorial Sleepiness Scale [PSS] was administered (self- and observer-rating, home and classroom) at several hours post-dose. Home assessments both self-rated and observer-rated, showed greater sleepiness in the guanfacine-treated group as compared to the placebo-group at the 12-hours post-dose evaluations at most visits. There were no dose-related trends but effects were more noticeable in the 6-12 year olds as compared to the 13-17 year olds.

The high incidence of hypno-sedative events and the detected sleepiness-effect in guanfacine-treated patients as compared to placebo-treated patients suggests effects on functions that require clarity of consciousness. In ADHD-patients symptoms of impulsivity and inattention may impair cognitive performance a priori, and hence treatment-associated reduction of those symptoms may enhance performance. In sum, the net result of ADHD-treatment using a hypno-sedative agent on cognitive function may be difficult to predict. This is in accordance with the study by Kugler et al, discussed in section 2.2.3, that suggest that the effects of guanfacine on cognitive performance differ for different tests. The validity of discrete cognitive tests, conducted in a highly controlled setting, for the prediction of long-term cognitive development was not considered satisfactory enough and the CHMP requested the applicant to perform a PASS to evaluate long-term cognitive development in ADHD patients treated with guanfacine.

Laboratory findings

The applicant reported no notable laboratory changes and no relevant differences between treatment-groups. However, increased blood glucose levels >160 mg/dL were observed in 14 patients (0.9%) treated using guanfacine (placebo: 0.1%, atomoxetine: 0.0%), while increased glucose was measured at baseline in only 3 guanfacine-treated patients (0.1%; placebo: 0.0%, atomoxetine: 0.0%).

Regarding haematology, in the case listings several cases of neutropenia appear in terms of absolute cell counts and percentage relative to total lymphocytes, among patients treated with guanfacine. As examples, patient 153-0004 had on day 50-54 of guanfacine-treatment a neutrophil count of 0.36 (normal range 1.65-8.15) and patient 009-0012 had a count dropping to 0.34 at day 50-56 of treatment using guanfacine. Patient 002-0007 had a neutrophils count of 0.18 at day 57-63 of treatment. In the overall pool, counts below 1.5 (moderate neutropenia) were slightly more frequent in patients using guanfacine (2.8%; placebo: 1.9%, atomoxetine: 2.1%). During the procedure the applicant specified the proportions of patients with very low counts (severe neutropenia) and the issue was considered as solved by the CHMP.

Cardiac effects

Cardiovascular effects were: lowering of blood pressure and pulse, and prolongation of QT-intervals. Effects on blood pressure are discussed in the section on serious adverse events (above).

A dose-dependent decrease in heart rate / pulse was observed, together with a dose-dependent prolongation of the QT-interval. In the overall pool, mean heart rate decreased 9.05 bpm (placebo: 1.06 bpm decrease, atomoxetine: 3.26 bpm increase). A total of 213 patients (10.8%) had a decrease of heart rate to a count of ≤50bpm at any time during guanfacine-treatment (placebo: 0.8%, atomoxetine: 1.0%).

Corrections were performed for the heart-rate associated prolongation of the QT-interval (Fridericia-correction, Bazett-correction). In the overall population, mean (SD) prolongation of QT-interval was 19.58 ms (26.704), median (min, max) prolongation was 19.00 ms (-90.3, 115.3). After Fridericia-correction prolongation was mean (SD) 3.96 ms (14.63) and median (min, max) 3.67 ms (-59.0, 66.0). After Bazett-correction prolongation was mean (SD) -4.95 ms (18.85) and median (min, max) -3.90 ms (-59.0, 66.0).

An on treatment QT-interval ≥480 ms was observed in 15 patients (0.8%) exposed to guanfacine, but not in patients exposed to either atomoxetine or placebo. After Fridericia-or Bazett-correction there were no intervals ≥500 ms.

In the overall pool, an on-treatment QT-interval prolongation ≥60 ms from baseline or more was observed in 276 patients treated using guanfacine (14.0%, placebo: 1.2%, atomoxetine: 0.0%). After Fridericia-correction a QT-interval prolongation ≥60 ms was observed in 5 patients using guanfacine (0.3%), and after Bazett-correction a QT-interval prolongation ≥60ms was observed in 7 patients using guanfacine (0.4%).

In the short-term fixed-dose study pool a dose-dependent decrease of heart rate and QT-interval prolongation was observed among guanfacine-exposed patients. In this pool a population-correction of QT-intervals was also performed.

In the short-term fixed dose pool, there were 3 guanfacine-exposed patients (0.7%) with population-adjusted QT-intervals ≥450ms, and no patients with QTcP ≥500ms. There were no QTcF prolongations ≥60ms and 1 patient (0.2%) with a QTcB prolongation ≥60ms. There were QTcF-interval prolongations between 30 and 60 ms showed a dose-response effect.

There were 5 patients with Fridericia-corrected QT-interval prolongations of 60ms or higher, which indicates impaired repolarisation and risk of arrhythmia due to guanfacine-treatment. Though the fixed-factor Fridericia correction-method may overestimate QT-intervals in case of lowered heart rates, the >60 ms prolongations are considered to be worrying.

Endocrinological adverse reactions

No safety concerns regarding endocrine function were identified, concerns regarding growth hormone and sex hormones were raised by the CHMP during the procedure and were satisfactorily adressed by the applicant.

Long-term safety

Mean BMI increased in the course of the long-term studies from 20.0 at baseline to 21.8 at month 24 (2.2 points mean increase in study completers) for patients who completed the 24-month study (all dose groups, n=60). This increase reflects a mean BMI percentile of 52.3% at baseline, and 62.4% at month 24 as compared to the age-matched population.

As BMI is known to be a predictor for weight-associated health problems in children and adolescents, the increase of 2.2 points over a 2-year treatment period is considered to be of serious concern. In published literature, a case was reported of a 9.53kg weight increase after a four-weeks guanfacine-treatment period (Khan et al, 2012). During the evaluation procedure the applicant was requested to elaborate on the risk of weight-associated adversity in long-term ADHD-treatment using guanfacine. In particular, the applicant submitted data regarding the proportion of patients with severe increases in BMI (>3 or 4) following 1 or 2 years of treatment who shift to the >85 or >95 percentile on normal BMI-for-age charts, coming from normal weight or slight overweight, i.e. the proportion of patients who become overweight or obese as a result of treatment.

Long-term cognitive effects of treatment using guanfacine were not evaluated. In view of the hypno-sedative adverse events and increased sleepiness reported in the trials, impaired learning ability (memory impairment), compromised school performance and delay of cognitive development cannot be excluded in children and adolescents, who are also at a-priori risk for delayed cognitive development due to the underlying ADHD disorder.

Therefore the CHMP requested the applicant to perform a PASS to evaluate long term safety of Intuniv.

Safety related to drug-drug interactions and other interactions

Three fatal cases of ADHD-patients treated with the combination of clonidine (i.e. (anti-)adrenergic compound similar to guanfacine) and methylphenidate were previously reported in published literature (Fenichel 1995). This combination was reported to increase PR-interval more than clonidine alone (Connor et al. 2000). A study combining treatment using guanfacine with several different psychostimulants, as a part of the currently submitted study-programme, did not reveal dissimilarities as compared to the safety profile of guanfacine mono-treatment. In this study 75 patients diagnosed with ADHD were treated with these combinations. Overall, 92.0% of patients treated with these combinations experienced TEAE's. There were no deaths or SAE's. TEAEs with highest incidence were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Irritability occurred notably more with co-administration of guanfacine with amphetamine (42.4%) as compared to methylphenidate (23.8%). Five patients (6.7%) discontinued study participation due to TEAE's. In three cases symptoms were dizziness, headache and somnolence. Overall, 56.0% of all treated patients experienced hypno-sedative TEAE's, most often with onset during treatment-week 2 or 3 and with average duration of one or two weeks. Somnolence was reported in 24.2% of the amphetamine-group and 14.3% of the methylphenidate-group. Regarding the TEAE sedation, average duration of this effect was longer in the amphetamine-group (23.0 days) as compared to the methylphenidate-group (6.0 days). One patient suffered severe TEAE's including fatigue, fecal incontinence, impaired balance and dizziness. Two patients had decreased white blood cell counts, including one patient with total count lowered to 3.89 and one patient with neutrophil count decreased to 1.28. There were 4 patients with elevated glucose levels during treatment.

During treatments there were decreases in blood pressure and pulse, with mean changes -4.7 / -2.0 mmHg and -2.8 / -6.4 bpm for methylphenidate / amphetamine. There were 4 patients with bradycardia (<50 bpm) in the methylphenidate-group. Low blood pressure was very common in the 13-17 years age-group. Three patients experienced clinically relevant decreased blood pressure /hypotension, and three patients experienced clinically relevant increased blood pressure or heart rate during the study. Regarding ECG parameters, corrected QT-interval prolongations were mild.

The interaction study is considered relevant for combination-therapy using a stimulant and guanfacine since this may be anticipated in clinical practice. In this study, clinically relevant vital abnormalities were typically mild, but 92% of all participating patients experienced TEAE's, and a total of 56% had hypno-sedative symptoms. Treatment combining guanfacine with psychostimulants can be foreseen to occur in clinical practice, but may not be well tolerated in most cases.

Post marketing experience

Guanfacine prolonged-release [GXR] (trade market Intuniv or Intunic XR) has been granted a marketing authorisation in 2 countries. The product was first approved on 02 September 2009 by the US FDA for the treatment of ADHD in patients 6 to 17 years of age. In Canada the product was approved on 05 July 2013 for the treatment of ADHD in children and adolescents ages 6 to 12 years. The product is currently marketed in the US and Canada.

The estimated patient exposure to GXR is 609360 person-years (PY) cumulatively since launch.
The estimated total of 2903 subjects exposed to the product in ongoing and completed clinical trials included 2346 pediatric subjects with ADHD, 62 subjects with anxiety disorders and 495 healthy volunteers. In completed clinical trials a total of 2028 subjects received GXR.

As part of this marketing authorisation application, the applicant submitted 7 PSURs of Intuniv (guanfacine prolonged release):

- PSUR 1, covering period 02 September 2009 – 01 March 2010, dated 16 April 2010
- PSUR 2, covering period 02 March 2010 – 02 September 2010, dated 21 October 2010
- PSUR 3, covering period 02 September 2010 – 01 March 2011, dated 15 April 2011
- PSUR 4, covering period 02 March 2011 – 01 September 2011, dated 17 October 2011
- PSUR 5, covering period 02 September 2011 – 01 March 2012, dated 20 April 2012
- PSUR 6, covering period 02 March 2012 – 01 September 2012, dated 23 October 2012
- PSUR 7, covering period 02 September 2012 – 01 September 2013, dated 24 October 2013

Changes to the reference safety information

On 25 February 2011, approval was obtained from the FDA for the additional indication for GXR to be used as adjunctive therapy with psycho stimulants.

Regulatory authority actions taken for safety reasons

On 20 February 2013, the US FDA requested the addition of the following post marketing events to the US Package Insert (USPI) based on the label of Tenex (guanfacine HCl): alopecia, alterations in taste, arthralgia, blurred vision, confusion, dermatitis, exfoliative dermatitis, dyspnea, edema, impotence, leg cramps, leg pain, malaise, myalgia, palpitations, pareasthesias, pruritis, rash, tachycardia, tremor and vertigo. The applicant has reviewed whether any of these 21 events meet the criteria to be included as an ADR into the Company Core Data Sheet (CCDS).

In May 2013, hallucinations were added to the USPI for GXR upon FDA request, and was included in the EU PI at CHMP request.

Safety issues

During the *first* PSUR period the applicant committed to monitor and evaluate the post marketing safety with a focus on sedative events, hypotension, bradycardia and syncope. In addition, the applicant was committed to expedite to the FDA all cases of syncope (n=11) and cases indicative of valvulopathy (n=0) due to binding to 5HT-2B receptors. No new safety concerns/signals were identified by the applicant in this PSUR period.

The applicant has implemented a RMP with a focus on syncope, hypotension, bradycardia and sedative events. Enhanced pharmacovigilance activities include the use of specific questionnaires.

During the *second* PSUR period for Intuniv the applicant closely monitored cases of syncope, hypotension, bradycardia, sedative events, and interaction with CYP3A4/5 inhibitors, withdrawal blood pressure increase and cardiac valvulopathy. One new safety topic for close monitoring – hyperglycaemia/diabetes mellitus – was added based on a published article reporting on inhibition of insulin secretion; no cases were identified for this risk.

During the *third* PSUR period initial hypertension after overdose was identified as a new safety risk based on 2 publications describing 1 case each of overdose with immediate release guanfacine. Initial hypertension was added to the Overdose section of the CCDS and USPI.

During the *fourth* PSUR period the applicant noticed that there were no changes to the risk assessment of the ongoing safety topics.

During the *fifth* PSUR period the safety topic inhibition of insulin secretion was closed by the applicant as there was no signal identified in patients treated with GXR. According to the applicant there were no changes to the remaining safety issues under closely monitoring.

During the *sixth* PSUR period, upon request of Health Canada, a cumulative review and analysis of all cases of QT prolongation and bradyarrhythmia, suicide-related events (SRE) and homicidal-related events (HRE) was completed. According to the applicant these reviews demonstrated that there is no evidence of effects on ventricular repolarization with GXR, and there is no association of SRE or HRE with GXR nor does SRE or HRE pose a potential risk for this product as evidenced by its pharmacological action. The applicant noticed that there were no changes to the remaining safety issues currently under closely monitoring.

During the *seventh* PSUR period an increasing cumulative number of post marketing cases reporting hallucinations were identified. Based on a cumulative review the applicant concluded that there was no causal relationship between the treatment with GXR and hallucinations. The FDA agreed that it has not been established that there is sufficient evidence of an association for hallucinations with GXR, however causality cannot be ruled out. Subsequently, upon the FDA's request, hallucinations was added to the adverse event post marketing section of the USPI, which was updated in August 2013. The applicant's position however has not changed and hallucinations have not been added in the CCDS.

Upon request of Health Canada a cumulative review through 01 October 2012 was conducted on the topic of QT effects and bradyarrhythmias in subjects treated with GXR. The applicant noticed that there is no evidence of any clinically meaningful effects on ventricular repolarization with GXR based on the cumulative review of safety data from clinical trials and post marketing reports, as well as a thorough QT/QTc study in healthy subjects. Bradyarrhythmias remain sufficiently described in the CCDS according to the applicant, and will continue to be monitored via routine pharmacovigilance and no additional activities are required at this time. No new safety signals were identified by the applicant during the seventh reporting PSUR period. There were 5 identified risks (Syncope, Bradycardia, Hypotension, Sedative events, Drug interaction with CYP3A4/5 inhibitors) and 2 potential risks (Withdrawal blood pressure increased, Cardiac valvulopathy due to binding to 5HT-2B receptors) with GXR.

Clinical studies

The ongoing study SPD503-315 is examining the long-term maintenance of efficacy and safety in children and adolescents with ADHD. As of 03 June 2013, enrolment phase of the study was completed and 528 subjects were enrolled. No new safety information was identified during this study.

Literature

The applicant included publications that described potential important new safety information related to GXR. One publication is summarized below.

Martinez J et al, 2013 reviewed the published evidence on the controversial association between medications approved for treating patients with ADHD and the risk of serious cardiovascular problems, specifically the risk of QTc prolongation and the risk of sudden cardiac death. *The authors* concluded that the risk for serious cardiovascular adverse events, including statistically or clinically significant increases in QTc and sudden cardiac death associated with α(2)-adrenergic agonists prescribed for ADHD is low and the benefits of treating individual patients with ADHD outweigh the risks. *The applicant* concluded that no new efficacy or safety information was appeared from this review paper and therefore does not impact the benefit risk ration of guanfacine.

The applicant stated that the benefit-risk profile of GXR for the treatment of ADHD is positive.

Cumulative PSUR data from all sources (spontaneous, authorities and literature) show 5,493 reported adverse events (451 serious and 5,042 non-serious). From non-interventional trials there were 3 serious adverse reactions cumulatively reported, from compassionate or solicited sources there were 40 adverse reactions cumulatively reported.

Most adverse reactions reported belong to the System organ class (SOC) Nervous system disorders (33.5%). The following table show the cumulative numbers of *serious* adverse reactions and preferred terms reported three (3) times or more:

System organ class (SOC) Preferred term	**Preferred term**	**Cumulative number of serious ADRs**
Nervous system disorders		**151 (33.5%)**
	Syncope	61
	Convulsion	21
	Loss of consciousness	20
	Somnolence	8
	Lethargy	7
	Dizziness	5
	Unresponsive to stimuli	4
	Grand mal convulsion	3
	Presyncope	3
Psychiatric disorders		**107 (23.7%)**
	Suicidal ideation	16
	Hallucination	15
	Psychotic disorder	8
	Homicidal ideation	6
	Aggression	5
	Hallucination, visual	5
	Hallucination, mixed	4
	Suicidal behaviour	4
	Suicidal attempt	4
	Hallucination, auditory	3
Vascular disorders		**39 (8.6%)**
	Hypotension	24
	Hypertension	5
Cardiac disorders		**38 (8.4%)**
	Bradycardia	18
	Sinus bradycardia	7
	Ventricular extrasystoles	3
Investigations		**28 (6.2%)**

System organ class (SOC) Preferred term	Preferred term	Cumulative number of serious ADRs
	Blood pressure decreased	6
	Blood pressure increased	4
	Heart rate decreased	4
	Heart rate increased	4
Injury, poisoning and procedural complications		**25 (5.5%)**
	Intentional overdose	10
	Toxicity to various agents	4
	Accidental overdose	3
General disorders and administration site conditions		**17 (3.8%)**
	Adverse event	5
Gastrointestinal disorders		**16 (3.5%)**
	Pancreatitis	4
Infections and infestations		**6**
Blood and lymphatic system disorders		**5**
Eye disorders		**4**
Metabolism and nutrition disorders		**4**
Skin and subcutaneous tissue disorders		**4**
Respiratory, thoracic and mediastinal disorders		**3**
Immune system disorders		**2**
Hepatobiliary disorders		**1**
Musculoskeletal and connective tissue disorders		**1**
Total		**451 (100%)**

The important identified risks (Syncope, Bradycardia, Hypotension, Sedative events, Drug interaction with CYP3A4/5 inhibitors, Withdrawal blood pressure increased) and important potential risks (, Cardiac valvulopathy due to binding to 5HT-2B receptors) will continue to be monitored through routine pharmacovigilance .

PSUR data show several serious adverse events, reported three times and more, which are not included in the proposed SmPC.

In SOC Blood and lymphatic system disorders, only isolated (n=1) adverse events were reported: anaemia, haemorrhagic diathesis, neutropenia, splenic vein thrombosis, thrombocytosis.

SOC Eye disorders include the following adverse events: blindness (n=1), blindness transient (n=2) and visual impairment (n=1).

No adverse events were reported belonging to SOC Neoplasm benign, malignant and unspecified (including cysts and polyps) and SOC Pregnancy, puerperium and perinatal conditions. Use in pregnancy is included as missing information in the proposed RMP. Blood glucose increased was not reported and weight increased was reported once cumulatively.

The above mentioned post marketing experience of guanfacine was taken into consideration to establish the benefit risk of guanfacine.

2.6.1. Discussion on clinical safety

A number of safety issues were identified, including low heart rate, low blood pressure and, in 16 guanfacin-treated patients, actual syncope's. Also, high rate of somnolence and sedation occurred, and some QT-interval prolongations were identified. Long-term data suggest serious risk of considerable weight gain. Insufficient data were submitted regarding long-term consequences of persistent hypno-sedation such as possible impaired cognitive development.

The active-comparator study (316) lists severe TEAE's to have occurred in 7.0% of guanfacine-treated patients (atomoxetine: 1.8%, placebo: 2.7%). As outlined in the applicants' response, TEAE's resulted in discontinuations in 7.9% of guanfacine-treated patients (atomoxetine: 4.5%, placebo: 0.9%). These

differences are considered to be substantial and question tolerability of guanfacine as compared to alternative treatments. The high rate of withdrawal (61.8%) observed in long-term studies raises questions on treatment adherence in clinical practice, outside the controlled research environment.

Tolerability of guanfacine-treatment is considered to be questionable regarding the observed frequencies of TEAE's. Premature discontinuations, attributed to TEAE's or overall, were more than twice as frequent among guanfacine-treated patients as compared to patients treated using atomoxetine. Severe TEAE's were recorded in excess of 4 times more often. The translation of these findings on treatment adherence in clinical practice, outside the controlled research environment, is of concern. Somnolence and sedation were reported by 50.8% of guanfacine-treated patients. In the short-term studies sedation-related symptoms led to study discontinuation in almost 12% of all guanfacine-treated patients, indicating severity and impact of those symptoms. Somnolence and sedation may be associated with the anti-adrenergic mechanism of action of guanfacine, as suggested by the observed dose-response relationship and the protracted duration of symptoms. They may impair school functioning, adding to possible learning impairments associated with the disorder itself. ADHD-treatment should typically be continued for a considerable time-span. Improvement of school-performance and cognitive development are major goals of ADHD-treatment. Against that background it is questioned whether guanfacine-treatment may accomplish such goals, considering the obvious adverse effect of somnolence and sedation on school performance and cognition. The applicant demonstrated adequately during the procedure that efficacy is acting at least for some part independently from reported sedation which gave some reassurance regarding this concern. Concerns regarding the risk of delay or deterioration of cognitive development of children and adolescents treated with guanfacine remain and the CHMP requested the applicant to perform a PASS study in order to evaluate the cognitive function of guanfacine-treated ADHD patients.

As expected regarding mechanism of action of guanfacine, effects include the cardiovascular effects of bradycardia and hypotension. Both in healthy volunteers and in treated ADHD-patients several syncopes occurred. This is considered to be an important concern. Syncope occurred in 16 guanfacine-treated patients (0.7%; placebo: 0.2%; atomoxetine: 0.0%). In the long-term studies syncope occurred in 7 patients (1.1%). Among 441 healthy (adult) volunteers, 2 subjects suffered syncope's. Among healthy volunteers enrolled in the QTc-study 3 subjects had syncope's. Syncope is a serious risk associated with falls, accidents and physical trauma in children and adolescents. In published literature, syncopes were also reported in patients receiving guanfacine-treatment for Tourette's syndrome (King et al, 2006). Syncope may increase risk of falls and (traffic-) accidents. Regarding reported frequencies of injury and accidents, the guanfacine-treatment associated risk (8.7 - 10.4%) is increased as compared to placebo (7.1%). It is noticed that the risk in atomoxetine-treated patients is low (1.8%) which may be associated with reduction of ADHD-symptoms such as impulsivity and inattention, possibly lowering the risk of accidents towards the level observed in the general (child and adolescent) population. Studies using long-acting methylphenidate containing products typically detect 1.3 – 4.4% of treatment-emergent injury; poisoning and procedural complications which is also substantially lower. ADHD-treatments may typically reduce ADHD-associated increase of injury, but this is questionable for guanfacine. Some data suggest that somnolence and sedation may be most pronounced at the start of treatment. This was further substantiated by the applicant, in particular regarding a possible association with the risk of hypotension. Sedation and in particular its potential implications in terms of cognitive impairment and neurocognitive development was of particular concern for the patient representatives and physicians who were consulted during this procedure.

The risk of potential pro-arrhythmic effect is also of concern. An on treatment QT-interval ≥480 ms was observed in 15 patients (0.8%) exposed to guanfacine, but not in patients exposed to either atomoxetine or placebo. There were 5 patients with Fridericia-corrected QT-interval prolongations of 60ms or higher.

In particular higher exposure after high-fat meals may increase that risk as suggested by prolongation of the corrected as well as uncorrected QT-intervals in the TQT-study. In the post-marketing experience as of Oct 2013, the applicant identified 4 cases of atrioventricular block or –dissociation, one case of bundle branch block and one case of atrial flutter. Regarding BMI, the applicant's responses confirmed the risk of severe weight gain in particular in the setting of long-term treatment using guanfacine.

Considering the above risks, recommendations with regard to dose titration and adjustment have been clearly described in section 4.2 of the SmPc and all the adverse reactions reported in clinical trials and post-marketing from the safety database have been also included in the SmPC.

The SmPC for Intuniv specifies in section 4.2 that treatment must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders, and according to national ADHD prescribing guidelines.

Educational materials were also developed to inform the specialist healthcare professionals about those risks, namely:

- A checklist prior to initiating treatment with Intuniv to identify patients at risk for serious undesirable effects;

- A checklist for ongoing monitoring and safety management of patients including titration phase during treatment with Intuniv;

- A chart for ongoing monitoring (vital signs, height, weight) of patients during treatment with Intuniv.

Lastly, in order to investigate the long term safety (especially effects on neurocognitive function) of Intuniv in Children and Adolescents Aged 6- 17 Years with ADHD, the CHMP requested the MAH to conduct and submit the results of a comparative safety study according to an agreed protocol.

2.6.2. Conclusions on the clinical safety

Important risks and uncertainties were identified for Intuniv, in particular bradycardia and hypotension causing syncope, accidents and injuries. Also pronounced somnolence and sedation and severe weight increase after prolonged treatment were of concern. Cases of severe weight increase after prolonged treatment were also noted. In order to minimise the risks and uncertainties, educational materials were developed to inform the healthcare professionals about these risks.

The safety of Intuniv was considered to be acceptable considering the restricted prescription status, the additional risk minimisation measures put in place as well as the condition to the marketing authorisation for the MAH to conduct a post-authorisation study in order to investigate the long term safety (especially effects on neurocognitive function) of Intuniv in Children and Adolescents Aged 6- 17 Years with ADHD.

Therefore the CHMP considered that appropriate measures were put in place to ensure safe use of the product in the recommended indication.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice.

The applicant provided an updated RMP version 1.6 addressing the PRAC advice comments.

The CHMP endorsed this advice with the following changes:

The CHMP made changes with regards to the wording of the Annex II condition to remove the duration of the study and the choice of comparator since these points need to be reviewed and agreed during a protocol assessment, the Annex II as agreed by CHMP is as follows:

In order to investigate the long term safety especially effects on neurocognitive function of Intuniv in Children and Adolescents Aged 6- 17 Years with ADHD, the MAH should conduct and submit the results of a comparative safety study, according to an agreed protocol.

The applicant indicated their intention to request Scientific Advice on the study protocol which was supported by the CHMP.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 1.6 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Bradycardia • Syncope • Hypotension/decreased blood pressure • Withdrawal blood pressure increase • Sedative events • Weight increase
Important potential risks	• Cardiac valvulopathy • QT prolongation • Off-label use • 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 and sexual maturation) • Drug interactions

Pharmacovigilance plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started**	**Date for submission of final reports (planned or actual)**
Drug utilisation study of INTUNIV (guanfacine extended release) in the European Union Category 3	**Primary objective:** To characterise patients who are prescribed guanfacine. To describe prescribing patterns of guanfacine among physicians.	Off-label use Effectiveness of the educational materials for healthcare professionals	Planned	Annual reports starting 1st year after approval (to coincide with PSUR)

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started	Date for submission of final reports (planned or actual)
	Secondary Objectives: To measure the effectiveness of the additional risk minimisation measure (educational materials for healthcare professionals) in order to assess compliance with the indication and with visits and measurements needed during the first year of treatment.			
SPD503-318: A Phase 3, Open-label, Multicentre, Protocol to provide access to Intuniv for European Children and Adolescents A+ged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) who participated in study SPD503-315 or SPD503-316 Category 3	**Primary objective:** To evaluate the long-term safety and tolerability of guanfacine **Secondary Objectives:** To provide the medicine to patients who participated in studies SPD503-315 or SPD503-316 To assess if the effectiveness of guanfacine achieved in the previous study is maintained	Long-term safety	Started	Submission of final study Report: 31-01-2016
SHP503-401: A Comparative Safety Study of Intuniv in Children and Adolescents Aged 6-17 Years with Attention-Deficit/Hyperactivity Disorder (ADHD) according to an agreed protocol Category 1	**Primary objective:** To investigate the long-term safety especially effects on neurocognition (assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) or any other scale as per current clinical guidelines. **Secondary objectives:**	- Long term safety (especially effects on neurocognition)	Planned	Submission of final protocol: 31 July 2016 Submission of final study Report: 31-01-2022

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started	Date for submission of final reports (planned or actual)
	To further characterise the risks of hypotension, syncope, sedative events, weight increase, bradycardia, growth, sexual maturation and QT prolongation. The study should have at least 2 year follow-up, or longer if needed for achieving study objectives.			
V7089M-SPD503: In vitro studies to identify transporter involved in hepatic uptake considering that metabolism accounts for more than 50% in the drug elimination. In addition, when a candidate transporter has been identified, an *in vivo* study with a strong inhibitor/inducer of the transporter at the site of interest is recommended, if feasible (see chapter 5.2.4. of the EMA guideline on drugdrug interactions) Category 3	To identify the transporter involved in hepatic uptake.	Potential drug interaction	Planned	Final study results: 31-03-2016
V7401M-SPD503: Time Dependent Inhibition study for the following: - CYP1A2, 2C9, 2C19, 2D6 and hepatic 3A4/5; - CYP2B6; - Intestinal CYP3A4, in line with the guideline on drug-drug interaction recommendations (e.g.	To identify if guanfancine is an inhibitor of CYP enzymes and drug transporters	Potential drug interactions	Planned	Final study results: 31-01-2016

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started	Date for submission of final reports (planned or actual)
inclusion of strong inhibitor, maximal intestinal exposure of the drug,i.e.10 µM, pre-incubation time of at least 30 min together with IC50 shift calculation is recommended in case of TDI); - Transporters BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 Category 3				
V7400M-SPD503: The MAH should re-perform the CYP induction study in line with the current EMA guideline on drug-drug interaction Category 3	To identify if guanfancine can induce CYP enzymes	Potential drug interactions	Planned	Final study results: 30-11-2015
The MAH should evaluate the pharmacological activity of 3-hydroxy guanfacine sulfate by in vitro assays. If 3-hydroxy guanfacine sulfate shows pharmacological activity in vitro, the enzyme involved in its formation should be identified. Category 3	To evaluate the pharmacological activity of 3-hydroxy guanfacine sulfate	Efficacy and potential interaction	Planned	Metabolite synthesis completed: 30-11-2015 Evaluation of Pharmacological activity: 28-02-2016

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Bradycardia	Pre screening and ongoing monitoring stipulation in Section 4.2 of the SmPC. Warnings and precautions in Section 4.4 of the proposed SmPC to measure patient's heart rate and blood pressure prior to initiation of treatment and periodically therafter.. Caution when	Educational materials for Healthcare professional

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	treating patients with a history of hypotension, heart block, bradycardia or cardiovascular disease. Caution when treating patients with a history of syncope or a condition that may predispose to syncope. Caution when treating patients concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Section 4.5 of the proposed SmPC recommends using caution when INTUNIV is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors. Bradycardia is listed as an ADR in Section 4.8 of the proposed SmPC.	
Syncope	Pre screening and ongoing monitoring stipulation in Section 4.2 of the SmPC. Warnings and precautions in Section 4.4 of the proposed SmPC to measure patient's heart rate and blood pressure prior to initiation of treatment and periodically thereafter. Caution when treating patients with a history of hypotension, heart block, bradycardia or cardiovascular disease. Caution when treating patients with a history of syncope or a condition that may predispose to syncope. Caution when treating patients concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Section 4.5 of the proposed SmPC recommends using caution when INTUNIV is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors. Section 4.7 warns of possible effects on the ability to drive and use machines. Syncope is listed as an ADR in Section 4.8 of the proposed SmPC.	Educational materials for Healthcare professional
Hypotension/decreased blood pressure	Pre screening and ongoing monitoring stipulation in section 4.2 of the SmPC. Warnings and precautions in Section 4.4 of the proposed SmPC to measure patient's heart rate and blood pressure prior to initiation of treatment. Caution when treating patients with a history of hypotension, heart block, bradycardia or cardiovascular disease. Caution when treating patients with a history of syncope or a condition that may predispose to syncope. Caution when treating patients concomitantly with antihypertensives or other medicinal products that can reduce blood pressure or heart rate or increase the risk of syncope. Section 4.5 of the proposed SmPC recommends using caution when Intuniv is administered to patients taking ketoconazole and other	Educational materials for Healthcare professional

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	strong CYP3A4/5 inhibitors. Hypotension and blood pressure decreased are listed as ADRs in Section 4.8 of the proposed SmPC.	
Withdrawal blood pressure increase	Section 4.2 of the proposed SmPC recommends monitoring blood pressure and pulse during dose downward titration (decrements of no more than 1mg every 3 to 7 days) and following discontinuation of Intuniv. Hypertension is listed as an ADR in Section 4.8 of the proposed SmPC.	Educational materials for Healthcare professional
Sedative events	Pre screening and ongoing monitoring stipulation in Section 4.2 of the SmPC. Warnings and precautions in Section 4.4 of the proposed SmPC to consider the potential of additive sedative effects before using with other centrally active depressants. Caution against the patient operating heavy equipment or driving until they know how they respond to treatment. Section 4.5 of the proposed SmPC recommends using caution when INTUNIV is administered to patients taking ketoconazole and other strong CYP3A4/5 inhibitors. Section 4.7 warns of possible effects on the ability to drive and use machines. Sedative events (somnolence, sedation, hypersomnia) are listed as ADRs in Section 4.8 of the proposed SmPC.	Educational materials for Healthcare professional
Weight increase	Pre screening and ongoing monitoring stipulation in Section 4.2 of the SmPC. Warnings and precautions in Section 4.4 recommends routine monitoring of height, weight and BMI.	Educational materials for Healthcare professional
Cardiac valvulopathy	None	None
QT prolongation	Pre screening and ongoing monitoring stipulation in Section 4.2 of the SmPC. Warnings and precautions in Section 4.4: Given the effect of INTUNIV on cardiac electrophysiology consider this observation in clinical decisions to prescribe INTUNIV to patients with a known history of QT prolongation, risk factors for torsades de pointes (e.g. heart block, bradycardia, hypokalemia) or patients who are taking medications known to prolongCaution in patients with known history of the QT prolongation, risk factors for torsades de pointes (e.g. heart block,	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	bradycardia, hypokalemia) or patients who are taking medicinal products known to prolong the QT interval. Recommends further cardiac evaluation based on clinical judgment. interval	
Off-label use	Use in children under 6 years, Adults and Elderly is addressed in Section 4.2 (Special populations) of the proposed SmPC	None
Blood glucose disorder	None	None
Use in pregnant or breastfeeding women	Pregnancy and breastfeeding are addressed in Section 4.6 of the proposed SmPC	None
Use in patients with renal or hepatic impairment	Use in patients with renal or hepatic impairment is addressed in Section 4.2 (Special populations) of the proposed SmPC	None
Long-term safety (especially effects on growth, sexual maturation and neurocognition).	Long-term safety is addressed in Section 4.2 of the proposed SmPC	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

The CHMP recommends the applicant to update the PL in order to maximise understanding of the product information (especially concerning key issues regarding safety and efficacy related to the chronic use of this product) by children and adolescents and therefore enhance treatment compliance in this special population. A dedicated user consultation with children and adolescents should be conducted on the updated PL.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, INTUNIV (GUANFACINE) is included in the additional monitoring list as there is an imposed PASS as an Annex II condition.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Guanfacine has shown to have a beneficial effect on symptoms of ADHD in children and adolescents as measured by the primary endpoint, ADHD-RS-IV. This was demonstrated in 4 short-term placebo controlled trials of 5-13 weeks duration (studies 301, 314, 312, and 316) and in a randomised withdrawal study of 6 months duration (study 315). In addition, the effect of guanfacine on symptoms was numerically higher compared to that of atomoxetine in the active-referenced study. The effect on symptoms was also demonstrated in the adolescents study (study 312).

Regarding functioning, statistically significant results were shown on WFIRS, on both the learning & school subscale (difference form placebo -0.22 (95% CI: -0.36 ; -0.08)) and the family subscale (difference from placebo -0.21 (95% CI: -0.36 ; -0.06)) in study 316. However, this effect was not replicated in studies 312 and 315. The effect of atomoxetine in study 316 was smaller, yet statistically significant for the learning & school subscale (difference form placebo -0.16 (95% CI: -0.31 ; -0.02) but not significant for the family subscale -0.09 (95% CI: -0.24 ; 0.06). Statistically significant effects were obtained on global measures such as CGI and PGA and on symptoms measures such as CPRS/CTRS.

Uncertainty in the knowledge about the beneficial effects.

It is expected that successful ADHD treatment will address not only symptomatic improvement but also alleviate impairment in functioning. There is uncertainty about the effect of guanfacine on functioning due to the fact that of the 3 studies that used a specific instrument to measure functioning, only one showed statistically significant results. While methodological weaknesses in the way functioning had been assessed in the studies may contribute to explain these results, the fact remains that an effect on functioning has not been consistently shown.

Significant effects were obtained on CPRS/CTRS, however this is a rating scale designed to evaluate DSM-IV ADHD symptoms rather than functioning. With respect to CGI and PGA, these are global measures of the patients' condition that may be influenced by either symptoms, functioning or both. Therefore, improvement on these scales may equally reflect improvement on symptoms and/or improvement in functioning.

Results showed that efficacy among patients with inattentive subtype ADHD is consistently lower than efficacy among patients with combined subtype ADHD. On the other hand, the applicant provided information showing that effects on the inattentive subscale of the ADHD-RS-IV were in the same order of magnitude as effects on the hyperactive subscale. It is difficult to know how this inconsistency should be interpreted.

Whether the effect of guanfacine is mediated only through sedation has been a matter of concern during the assessment, also in view of the lack of effect on functioning. Analyses stratified for patients who did and who did not report sedation as an AE were performed to address this concern. In the pooled data from studies 301 and 304 the effect size in the subgroup with sedative AEs was smaller than in the subgroup without sedative AEs (0.17 vs 0.49 respectively). Although this may be explained by the high placebo response in the subgroup with sedative AEs, the higher placebo response in the subgroup with sedative AEs may actually support the hypothesis that sedation drives the reduction in ADHD symptoms. On the other hand, additional analyses provided do not support such hypothesis. Indeed, the drop-out rates in the two subgroups (with and without sedative AEs) were similar and the proportion of responders increases with time while sedative AEs are observed mainly in the first weeks of treatment. In the randomized withdrawal study 315, with balanced randomization for sedative AEs between the INTUNIV and placebo group, the difference in failure rate in the placebo vs INTUNIV treated subgroup was 13% in favour of INTUNIV (66.7% vs 53.7% in the placebo vs. INTUNIV, respectively) while in the subgroup without sedative AEs the difference was 19% in favour of INTUNIV (62.9% vs 44.1%). Though in both cases the difference was not statistically significant, the larger difference in favour of INTUNIV in the non-sedated patients suggests that sedation did not drive the effect in the randomised withdrawal trial. The treatment effect sizes were comparable between the subgroup with and without sedative AEs (0.47 and 0.51 respectively). The additional data show that an efficacy on ADHD symptoms has been observed also in subjects without reported sedation. No clear temporal relationship between efficacy and reporting of this AE has been demonstrated. This suggests that although contribution of sedation to the reduction on the symptom scale cannot be completely excluded, efficacy may be achieved at least partially via a different mechanism of action.

Risks

Unfavourable effects

Bradycardia and hypotension, syncope

As expected, given the mechanism of action of guanfacine, effects include the cardiovascular effects of bradycardia and hypotension. In the overall pool of guanfacine-treated patients, bradycardia occurred in 1.5%, hypotension in 3.2% and syncope occurred in 0.7% of all guanfacine-treated patients. Syncope occurred in 16 guanfacine-treated patients (0.7%; placebo: 0.2%; atomoxetine: 0.0 Syncope is a serious risk associated with falls, accidents and physical trauma hazard in children and adolescents. In published literature, syncopes were also reported in patients receiving guanfacine-treatment for Tourette's syndrome (King et al, 2006). Injury and accidents was reported more frequently with guanfacine-treatment (10.4%) than with placebo (7.1%). It is noticed that the risk in atomoxetine-treated patients is low (1.8%) which may be associated with reduction of ADHD-symptoms such as impulsivity and inattention, possibly lowering the risk of accidents towards the level observed in the general (child and adolescent) population. Studies using long-acting methylphenidate containing products typically detect 1.3 – 4.4% of treatment-emergent injury; poisoning and procedural complications which is also substantially lower. ADHD-treatments may typically reduce ADHD-associated increase of accident-proneness and injury, but this is questionable for guanfacine.

Somnolence and sedation

Somnolence and sedation were reported by 50.8% of guanfacine-treated patients. The occurrence of somnolence and sedation was most prominent in the first few weeks of treatment and diminished gradually thereafter.

Weight increase

In the overall pool of guanfacine-treated patients, weight increases occurred in 2.9% of patients. An age- and sex-normalised mean change from baseline in BMI percentile of 4.3 over 1 year was observed A considerable proportion of those patients shifted to the >85th and >95th percentile in normal BMI-by-age charts starting at normal or slightly above average weight, i.e. became overweight or obese due to treatment.

QT prolongation

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

In view of the risks above, prior to prescribing, it is necessary to conduct a baseline evaluation to identify patients at increased risk of somnolence and sedation, hypotension and bradycardia, QT-prolongation arrhythmia and weight increase /risk of obesity as described in the SPC sections 4.2 and 4.4. The SPC also gives recommendations for monitoring during dose titration and thereafter. In addition, patients are advised against operating heavy equipment, driving or cycling until they know how they respond to treatment with Intuniv, as described in section 4.7 of the SPC. Dedicated educational materials for healthcare professionals have also been developed to support the safe use of Intuniv.

Uncertainty in the knowledge about the unfavourable effects

Somnolence and sedation

Somnolence and sedation may result in impaired school performance and delayed cognitive development. ADHD-treatment should typically be continued for a considerable time-span, but long-term cognitive effects of treatment using Intuniv were not evaluated. Impaired learning ability (memory impairment) and delay of cognitive development cannot be excluded. Long term effect of Intuniv on cognitive function will be investigated in a PASS in children and adolescents with ADHD.

QT prolongation

Prolongation of the corrected QT-interval was observed in the withdrawal-phase but it remains unclear whether that effect includes an increased risk of TdP or life-threatening arrhythmias.

Weight increase

The applicant submitted the results of an epidemiological population-based study that showed no effect on BMI, but the differences between these findings as compared to the results of the long-term studies are poorly understood. A considerable – but partly uncertain - proportion of the increases in BMI in the long-term studies were associated with shifts to the >85% or >95% percentile of normalised BMI-for-age curves for patients with normal weight or slightly overweight at baseline (onset of overweight or obesity due to treatment). In the long-term studies, duration of exposure to higher recommended dose-levels was limited due to a high rate of premature discontinuations. Therefore safety of long-term exposure to guanfacine, in particular regarding weight-gain, remains uncertain. Therefore, monitoring of height, weight and BMI should be done prior to initiation of therapy and then every 3 months for the first year, taking into consideration clinical judgement. 6 monthly monitoring should follow thereafter, with more frequent monitoring following any dose adjustment.

General tolerability and adherence to treatment

TEAE's resulted in discontinuations in 7.9% of guanfacine-treated patients (atomoxetine: 4.5%, placebo: 0.9%). Regarding the long-term studies the high rate of withdrawal (61.8%) leaves doubts whether in clinical practice, outside the controlled research environment, treatment adherence will be sufficient for feasibility of long-term therapy that is typically required in ADHD-treatment.

Effects Table

Table 8. Effects Table for Intuniv in the treatment of ADHD in children aged 6-17 years old (studies 312 and 316).

Effect	Short description	Unit	Intuniv dose	improvement from baseline [range]	Atomox	Placebo	Uncertainties/ Strength of evidence	Ref
Favourable effects Short-term								
ADHD-RS-IV	Mean improvement on ADHD-RS-IV vs baseline (ADHD-RS-IV measures symptoms severity)	Unit points	1 mg[1] 2 mg[2] 3 mg[2] 4 mg[2] 1-7 mg	- 20.4 [-15.4- -18.0] [-15.8- -19.4] [-19.0- -20.9] [-23.9- - 25.7] [4]	-18.6 (11.9)[5]	[-8.9 - -19.5]	Statistically significant effects in all studies. Mean effect sizes in the short-term studies were, Study 301: 0.4; Study 304: 0.5; Study 316: 0.7 Study 312: 0.5. Overall effect size: 0.5. This effect size is smaller than the effects usually seen for MPH. Dropout in the studies was > 1/3. Responders not a priori defined in protocol. Effect not found in inattentive subtype of ADHD	1,2
								4, 5
Responders	Responders defined as ≥ 25% reduction in ADHD-RS-IV	%	1 mg[3] 2 mg[3] 3 mg[3] 4 mg[3] 1-7 mg	73.7 69.8 75.0 81.1 [64.3-66.9][4]	55.4[5]	[42.3-57.1[3]		3
								4
WFIRSP l&s	Mean improvement on WFIRSP learning&school (WFIRSP measures functioning in various area such as school and family).	Unit points	1-7 mg[4]	[-0.57- -0.64]	-0.58	[-0.42- -0.46]	Effects on functioning were not consistently demonstrated.	4
WFIRSP fam	Mean improvement on WFIRSP family	Unit points	1-7 mg[4]	[-0.37- -0.62]	-0.50	[-0.31- -0.41]		4
Favourable effects Randomised withdrawal study								

ADHD-RS-IV	Mean improvement on ADHD-RS-IV vs baseline (SD)	Unit points	1-7 mg[6]	9.6 (11.5)		15.9(14.2)	Dropout in randomised withdrawal study >50% in the active arm and most occurred in the first month of treatment, shedding doubt on ability to comply with medication.	6
Tx failure	Treatment failure	%	1-7 mg[6]	49.3		64.9		6
WFIRSP l&s	Mean improvement on WFIRSP learning&school	Unit points	1-7 mg[6]	0.24		0.38	Effects on functioning were not demonstrated.	6
WFIRSP fam	Mean improvement on WFIRSP family	Unit points	1-7 mg[6]	0.24		0.31		6

Effect	Short description	Unit	Intuniv Dose		Atomox	Placebo	Uncertainties/ Strength of evidence	Ref
Unfavourable effects								
Somnolence	Incidence of somnolence	%	1 mg 2 mg 3 mg 4 mg	26.2 20.7 28.5 39.7	17.9	10.0	The most important safety issues associated with guanfacine are somnolence/sedation and syncope. These unfavourable effects are considered to be pharmacologically associated and together constitute the most important risk for the safety of children and adolescents due to risk of accidents and falls causing injury.	7
Sedation	Incdence of sedation	%	1 mg 2 mg 3 mg 4 mg	1.6 10.0 9.9 13.2	1.8	2.0		7
Syncope	Incidence of syncope	%	1-7 mg	0.7	0.0	0.0		8
Injury	Incidence of injury	%	1-7 mg	10.4	1.8			8
QT prolongation	Incidence of ΔQT>60 ms	%	1-7 mg	14.0	0.0	1.2	Persisting prolongations after corrections, bradycardia frequent, risk TdP unknown	8
BMI increase	BMI increase	Unit points	1 mg 2 mg 3 mg 4 mg	3.9 1.3 2.2 2.4			Clear increase over time, proportion severe increase unknown, high dropout rate	9

			1-7mg	2.2				

Abbrevations : ADHD-RS-IV:Attention Deficit and Hyperactivity Disorder Rating Scale according to DSM-IV criteria; WFIRSP: Weiss Functional Impairment Rating Scale; Resp: Responders defined as a ⩾30% reduction from baseline in the ADHD-RS-IV and a CGI-I of 1 or 2.Tx failure, defined as 2 consecutive weeks with an increase of >50% in ADHD-RS-IV and an increase of > 2-points in CGI-S score relative to baseline of the randomised withdrawal Phase;
Notes [1] Study 304 (mean difference (SD) [2] Studies 301, 304 [range], [3] Study 304, [4]Study 312, 316, [5]Study 316, [6]Study 315 withdrawal
[7] Randomised pool, [8]overall pool, [9]Long term studies

Benefit-risk balance

Importance of favourable and unfavourable effects

ADHD is one of the most common neurodevelopmental disorders of childhood. It is a well-defined disorder with core features of inattention, hyperactivity, and impulsivity, but also impairment in executive functions. Treatment is therefore directed towards improvement of attention and reduction of hyperactivity/impulsivity in order to be able to focus on tasks and performance, and improve associated behavioural and relational problems.

As underlined by consulted experts, the improvement in ADHD symptoms in children and in adolescents is considered to be an important step in the management of the disorder. Therefore, the effect of Intuniv on symptoms was considered clinically meaningful by the CHMP, despite the lack of effect on functioning (both at school and at home).

The most important safety issues associated with guanfacine are bradycardia, hypotension, syncope, somnolence and sedation. These unfavourable effects are considered to be pharmacologically associated and together constitute the most important risk for the safety of children and adolescents due to risk of accidents and falls causing injury. In addition, the risk of increased BMI is an important unfavourable effect that may lead to mental and physical health problems on the long term. Appropriate measures including additional pharmacovigilance activities and risk minimization measures were put in place to help ensure safe and effective use of the product in the recommended indication.

Discussion on the benefit-risk balance

Guanfacine HCl is a selective alpha2–adrenergic agonist. Its hypothesised mechanism of action is the modulation of the noradrenergic tonus of the pyramidal cells in the prefrontal cortex, thereby restoring deficits in attention and impulse control. It is a new class of medication for ADHD, which is different from the mechanism of action of existing medication

Intuniv has shown an effect on symptoms. This effect was consistently statistically superior to placebo across pivotal studies, and numerically superior to that of atomoxetine in the only active-referenced trial. The lack of effect on functioning was carefully considered by the CHMP and a scientific advisory group in psychiatry (SAG) was convened to help explore the relevance of the benefits seen with Intuniv. The SAG underlined the methodological difficulties pertinent to the measurement of functioning in psychiatric disorders and in ADHD in particular. As such, an inconsistent effect on WFRIS may not be interpreted as a failure of improvement of functioning in general according to the SAG experts. The SAG also considered that ADHD treatment is multifaceted and that the reduction of symptoms is to be considered as a first step in the management of the disorder. In psychiatric disorders in general, symptom reduction is of importance to minimize burden of the disorder and to enable the patient to recover in his/her functioning level. Therefore, the observed efficacy of Intuniv on symptoms of ADHD, even though seemingly modest, was considered as clinically relevant in itself by the SAG experts. This view was supported by patients' representatives who considered the effects on symptoms as a first step towards revovery. It was indeed acknowledged that symptom relief may help to improve the way the ADHD children/adolescent interacts with its environment, thereby improve their self-perception and give them a chance to move on towards recovery. However, patient representatives highlighted that the second step should be an improvement on functioning at school, home and in the daily activities.

Sedation and somnolence induced by Intuniv were also very carefully considered by the CHMP and subject to a consultation of the SAG psychiatry and patient's representatives. There were concerns in particular that sedation may drive the effect of Intuniv on symptoms. Although the role of sedation on symptom control cannot be excluded, this concern was alleviated by the lack of temporal relationship observed in

the trials between the sedation SAEs and the effects on core symptoms of ADHD, which would not be consistent with a simple sedative effect of the medication. However, somnolence and sedation were considered to be important risks by the CHMP, the SAG psychiatry and the patients' representatives. According to the patients representatives who were consulted during the procedure, sedation and its potential consequences on neurocognitive development were of particular concern from the safety perspective. Together with the risk of bradycardia, hypotension and syncope, somnolence and sedation carry also the risk of accidents and falls causing injury. Evening sedation may also not be acceptable for some patients and their families as evening is a time for family life and after school activities. On the other hand, it was acknowledged that sedation may be beneficial for some patients with sleep problems, as from the clinical perspective, sedation may help in some cases to manage symptoms such as agitation. In view of the important identified and potential risks of Intuniv, appropriate measures including additional pharmacovigilance activities and risk minimization measures were put in place to help ensuring safe and effective use. These include detailed dosing instructions and warnings and precautions for use in the labelling, as well as dedicated educational materials for prescribers for pre-treatment screening, dose titration and monitoring of patients. In addition the applicant committed to conducting a long-term comparative post-authorisation safety study investigating the long term safety, especially the effects on neurocognitive function, of Intuniv in children and adolescents with ADHD. The MAH should conduct and submit the results of the safety study, according to an agreed protocol and the CHMP. Adherence to long-term treatment in the real clinical setting was also identified as a possible difficulty, in view of the high rate of withdrawal (61.8%) observed in the long-term.

The CHMP discussed the ADHD population that could benefit the most from treatment with Intuniv. It is acknowledged that methylphenydate has a more consistent and larger effect in symptom reduction than guanfacine (d=0.8 compared to d=0.5). Also, improved social- and school-functioning has been shown for treatments using short- or long-acting MPH-containing products. Clinical experts consulted during the procedure considered that treatment with stimulants has to be considered as fist line treatment due to their higher efficacy. However, the need to have alternative therapeutic options to stimulants was also underlined, and so was the existence of cases where Intuniv may be the most appropriate treatment due for example to specific clinical features of the patients (e.g. comorbidities such as tics, weight loss or insomnia) or clear contraindications to stimulants. Apart from those cases, Intuniv will be used as further line therapy. As such, Intuniv offers a different mechanism of action than atomoxetine, to which it compared favourably with atomoxetine in the active-referenced study (d=0.5 compared to d=0.3) in terms of symptoms control, although this study was not powered initially to show a difference between the two medicines.

In conclusion, the CHMP considered that Intuniv should be indicated for children and adolescents for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. It also considered that both children and adolescents should be eligible for treatment, as the evidence available was eventually considered to be sufficient for children less and above 12 years old, and also considering that there would be no pharmacological or clinical rationale for stopping the medication at the age of 12, as underlined by the SAG psychiatry.

Importantly, the CHMP concurred also with the SAG experts view - also expressed by patient representatives - that the treatment of ADHD should be multifactorial. This is duly reflected in the indication wording whereby Intuniv must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures. Like for other medicines approved for the treatment of ADHD, Intuniv is not indicated in all individuals with ADHD and the decision to use Intuniv must be based on a thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age. Diagnosis should be made according to DSM criteria or the current guidelines in ICD and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom. The specific aetiology of ADHD is

unknown and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational and social resources. For this reason, the SPC for Intuniv specifies in section 4.2 that treatment must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders, and according to national ADHD prescribing guidelines.

Benefit-risk balance

In light of the totality of the evidence and taking into account the experts' view, the CHMP concluded that the benefits of Intuniv outweighed its risks in the treatment of attention deficit/ hyperactivity disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive) for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Thus, the benefit-risk balance was considered favourable provided that adequate risk minimisation measures are in place.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Intuniv in the following indication:

Intuniv is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 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.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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

RMP.

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to launch of Intuniv in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

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

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

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

- Information on the risks associated with Intuniv: Bradycardia, Syncope, Hypotension/decreased blood pressure, Withdrawal blood pressure increase, sedative events and weight increase
- Checklist prior to initiating treatment with Intuniv to identify patients at risk for serious undesirable effects
- Checklist for ongoing monitoring and safety management of patients including titration phase during treatment with Intuniv
- Chart for ongoing monitoring (vital signs, height, weight) of patients during treatment with Intuniv

- **Obligation to complete post-authorisation measures**

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

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable

These conditions reflect the advice received from the PRAC with the exception of modification in the imposed post-authorisation safety study, as discussed in section 2.7.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0265/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

APPENDIX 1

DIVERGENT POSITION DATED 23 JULY 2015

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Intuniv, indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 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.

The overall benefit-risk balance for Intuniv in the claimed indication is considered negative due to:

- moderate and inconsistent efficacy on ADHD symptoms
- questionable effect on functioning
- prominent safety risks, especially sedation, bradycardia, hypotension, syncope
- concerns about the long-term use on cognitive development, BMI and sexual maturation

Overall, for these reasons, I consider that the benefit/risk ratio is negative for Intuniv in the claimed indication:

Intuniv is indicated for treatment of ADHD in children and adolescents 6 to 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.

London, 23 July 2015

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Pierre Demolis