EU Risk Management Plan
for
Paxneury (guanfacine)

RMP version to be assessed as part of this application:

RMP version number: 0.3

Data lock point for this RMP: 31 May 2024

Date of final sign-off: 29 November 2024

Rationale for submitting an updated RMP: Not applicable.

Summary of significant changes in this RMP: Not applicable.

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP: Not applicable.

QPPV name: Lucía Castrillo Soto

Table of contents

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ATC	Anatomical Therapeutic Chemical classification
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - human
EEA	European Economic Area
EM	Educational Material
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GFR	Glomerular Filtration Rate
GVP	Good Pharmacovigilance Practices
INN	International Non-proprietary Name
LQTS	Long QT Syndrome
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PASS	Post-Authorisation Safety Study
PL	Package Leaflet
QPPV	Qualified Person for Pharmacovigilance
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) (INN or common name)	Guanfacine
Pharmacotherapeutic group(s) (ATC Code)	Antihypertensives, antiadrenergic agents, centrally acting (ATC code:C02AC02).
Marketing Authorisation Applicant	Neuraxpharm Pharmaceuticals, S.L.
Medicinal products to which this RMP refers	7.
Invented name(s) in the European Economic Area (EEA)	Paxneury
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/0006312).
Brief description of the product	**Chemical class:** Guanfacine is a selective ά-A_2 adrenergic receptor agonist [**Error! Reference source not found.**, 2023], in that it has 15-20 times higher affinity for this receptor subtype than for the ά-$_{2B}$ or ά-$_{2C}$ subtypes.
	Summary of mode of action: The mode of action of guanfacine in Attention Deficit Hyperactivity Disorder (ADHD) is not fully established. Pre-clinical research suggests guanfacine modulates signalling in the prefrontal cortex and basal ganglia through direct modification of synaptic noradrenalin transmission at the ά-$_{A2}$ adrenergic receptors.
	Important information about its composition: Not applicable.
Hyperlink to the Product Information	Please refer to the product information text in module 1.3.1.
Indication(s) in the EEA	**Current:** Guanfacine is indicated for the treatment of ADHD in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. It must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures.
	Proposed: Not applicable.

Dosage in the EEA

Current:

For oral administration.

The *recommended starting dose* is 1 mg of guanfacine, once a day (the dose may be adjusted in increments of not more than 1 mg per week).

The *recommended maintenance dose* is 0.05-0.12 mg/kg/day.

Dose should be individualised according to the patient's response and tolerability.

Paediatric population

Dose titration schedule for children aged 6-12 years				
Weight Group	**Week 1**	**Week 2**	**Week 3**	**Week 4**
25 kg and up Max Dose= 4 mg	1 mg	2 mg	3 mg	4 mg

Dose titration schedule for adolescents (aged 13-17 Years)							
Weight Group[a]	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**
34-41.4 kg Max Dose= 4 mg	1 mg	2 mg	3 mg	4 mg			
41.5-49.4 kg Max Dose= 5 mg	1 mg	2 mg	3 mg	4 mg	5 mg		
49.5-58.4 kg Max Dose= 6 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	
58.5 kg and above Max Dose= 7 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg[b]

[a] *Adolescent subjects must weigh at least 34 kg.*

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

Proposed:

Not applicable.

Pharmaceutical form(s) and strengths	**Current:** Prolonged-release tablets. Each tablet contains 1 mg/2 mg/3 mg/4 mg/5 mg/6 mg/7 mg of guanfacine.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes.

Part II: Safety specification

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

Not applicable since this module is not required for hybrid type of application.

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

Not applicable since this module is not required for hybrid type of application.

Part II: Module SIII - Clinical trial exposure

Not applicable since this module is not required for hybrid type of application.

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

Not applicable since this module is not required for hybrid type of application.

Part II: Module SV - Post-authorisation experience

Not applicable since this module is not required for hybrid type of application.

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

Not applicable since this module is not required for hybrid type of application.

Part II: Module SVII - Identified and potential risks

Not applicable since this module is not required for hybrid type of application if the originator product has an RMP or the safety concerns are published by the CMDh.

Part II: Module SVIII - Summary of the safety concerns

This summary of safety concerns has been obtained from the European Public Assessment Report (EPAR) - Summary of the RMP for Intuniv® (Takeda Pharma AG) (the originator pharmaceutical product) updated on 09 May 2024 on the European Medicines Agency (EMA) website.

Table SVIII.1: Summary of safety concerns

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

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

III.1 Routine pharmacovigilance activities

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are in place for the products included in this RMP.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned or ongoing by the Company.

However, a Post-Authorisation Safety Study (PASS) (**SHP503-401:** *A Comparative Safety Study of INTUNIV in Children and Adolescents Aged 6-17 Years with ADHD according to an agreed protocol*), has been imposed to the originator pharmacological product (Intuniv®; Takeda Pharma AG). The objective of this study is to investigate the long term safety (especially effects on neurocognitive function, growth, and sexual maturation) of the product in children and adolescents aged 6-17 Years with ADHD. The submission of final study report is set on 31 January 2028. The Company will update and integrate the results of the PASS into the product safety if required.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No planned or on-going post-authorisation efficacy studies have been imposed.

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

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

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

Safety concern	Routine risk minimisation activities
QT prolongation	Routine risk communication: *SmPC section 4.2.* *SmPC section 4.4.* *SmPC section 4.5.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *As per section 4.2 and 4.4 of the SmPC, a baseline evaluation to identify patients at increased risk of QT-prolongation arrhythmia is required prior the initiation of the treatment.* *Section 4.4 of the SmPC: recommends caution in patients with a known history of QT prolongation, risk factors for torsade de pointes (e.g., heart block, bradycardia, hypokalaemia) or patients who are taking medicinal products known to prolong the QT interval. These patients should receive further cardiac evaluation based on clinical judgement.* *Section 4.5: of the SmPC states that concomitant use of guanfacine with QT prolonging medicinal products is generally not recommended.* Other routine risk minimisation measures beyond the Product Information: *Legal status: prescription only medicine.*
Use in pregnant or breastfeeding women	Routine risk communication: *SmPC section 4.6.* *PL section 2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.6 of the SmPC: states that use of guanfacine during pregnancy and in women of childbearing potential not using contraception is not recommended. Besides, it is informed that a risk on the breast-fed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue and/or abstain from guanfacine therapy taking into account the*

Safety concern	Routine risk minimisation activities
	benefit of breast feeding for the child and the benefit of therapy for the woman. *PL section 2 states that the intake of the product is not recommended if you are pregnant or not using contraception and if you are breast-feeding.* Other routine risk minimisation measures beyond the Product Information: *Legal status: prescription only medicine.*
Use in patients with hepatic or renal impairment	Routine risk communication: *SmPC section 4.2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.2 of the SmPC states that a dose reduction may be required in patients with different degrees of hepatic and severe renal impairment; end stage renal disease (GFR<15 ml/min) or requiring dialysis, and that the impact of hepatic impairment on the pharmacokinetics of guanfacine in paediatric patients (children and adolescents 6-17 years old) was not assessed.* Other routine risk minimisation measures beyond the Product Information: *Legal status: prescription only medicine.*
Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation).	Routine risk communication: *SmPC section 4.2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.2 of the SmPC: It is advised that patients should be re-evaluate the usefulness of the medication when guanfacine used for extended periods (over 12 months)..* Other routine risk minimisation measures beyond the Product Information: *Legal status: prescription only medicine.*

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of Risk Minimisation Measures

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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
QT prolongation	Routine risk minimisation measures: *SmPC section 4.2.* *SmPC section 4.4.* *SmPC section 4.5.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in pregnant or breastfeeding women	Routine risk minimisation measures: *SmPC section 4.6.* *PL section 2.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in patients with hepatic or renal impairment	Routine risk minimisation measures: *SmPC section 4.2.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	Routine risk minimisation measures: *SmPC section 4.2.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Part VI: Summary of the risk management plan

Summary of risk management plan for Paxneury (guanfacine)

This is a summary of the Risk Management Plan (RMP) for Paxneury. The RMP details important risks of Paxneury, how these risks can be minimised, and how more information will be obtained about Paxneury's risks and uncertainties (missing information).

Paxneury's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Paxneury prolonged-release tablets should be used.

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

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

I. The medicine and what it is used for

Paxneury is authorised for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective (see SmPC for the full indication). It contains guanfacine as the active substance and it is given by oral route of administration.

Further information about the evaluation of Paxneury's benefits can be found in Paxneury's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <Paxneury | European Medicines Agency (EMA) >.

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

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

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

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

Together, these measures constitute ***routine risk minimisation measures***.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

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

II.A List of important risks and missing information

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

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

II.B Summary of important risks

QT prolongation	
Evidence for linking the risk to the medicine	Overall based on the cumulative review of safety, QT prolongation has been reported in clinical trials studies and post-marketing reports.
Risk factors and risk groups	Risk factors for that have been identified in children include female gender, age, prior syncopal history, QT-interval duration, and genetic/familial factors. Most research in this area has focused upon the risk factors for serious cardiac events following diagnosis of Long QT Syndrome (LQTS).
Risk minimisation measures	Routine risk minimisation measure: *SmPC section 4.2.* *SmPC section 4.4.* *SmPC section 4.5.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*

Use in pregnant or breastfeeding women	
Risk minimisation measures	Routine risk minimisation measure: *SmPC section 4.6.* *PL section 2.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*

Use in patients with hepatic or renal impairment	
Risk minimisation measures	Routine risk minimisation measure> *SmPC section 4.2.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*

Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	
Risk minimisation measures	Routine risk minimisation measure: *SmPC section 4.2.* *Legal status: prescription only medicine.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *See section II.C of this summary for an overview of the post-authorisation development plan.*

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Paxneury.

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

There are no studies required for Paxneury.

However, a Post-Authorisation Safety Study (PASS) (**SHP503-401:** *A Comparative Safety Study of INTUNIV in Children and Adolescents Aged 6-17 Years with ADHD according to an agreed protocol*), has been imposed to the originator pharmacological product (Intuniv®; Takeda Pharma AG). The objective of this study is to investigate the long term safety (especially effects on neurocognitive function, growth, and sexual maturation) of the product in children and adolescents aged 6-17 Years with ADHD. The submission of final study report is set on 31 January 2028. The Company will update and integrate the results of the PASS into the product safety if required.

Part VII: Annexes

Table of contents

Annex 4 – Specific adverse drug reaction follow up forms

Not applicable.

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

Not applicable.