Swiss Summary of the Risk Management Plan (RMP) for Guanfacine (INTUNIV)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risk as well as to prevent or minimize them.

The RMP summary of INTUNIV is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of INTUNIV in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of INTUNIV.

Summary of risk management plan for INTUNIV (Guanfacine)

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

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

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

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

I. The medicine and what it is used for

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

Further information about the evaluation of INTUNIV's benefits can be found in INTUNIV's EPAR, including in its plain-language summary, available on the EMA website.

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

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

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

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

Together, these measures constitute routine risk minimisation measures.

In the case of INTUNIV, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

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

II.A List of important risks and missing information

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

evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Bradycardia • Syncope • Hypotension/decreased blood pressure • Withdrawal blood pressure increase • Sedative events • Weight increase
Important potential risks	• QT prolongation • Off-label use
Missing information	• Use in pregnant or breastfeeding women • Use in patients with hepatic or renal impairment • Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)

II.B Summary of important risks

Important Identified Risk: Bradycardia	
Evidence for linking the risk to the medicine	Bradycardia has been reported in clinical trials, post marketing surveillance and scientific literature.
Risk factors and risk groups	Patients who may be taking concomitant medications that can increase the rate and extent of guanfacine exposure may be at an increased risk. In general, age and co-morbid cardiac conditions are key risk factors for bradycardia. Smoking, stress, and anxiety may also increase the risk of bradycardia.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 – Recommendations to conduct a baseline evaluation at pre-treatment screening, a dose titration and ongoing monitoring SmPC Section 4.4 – Recommendations to monitor heart rate and blood pressure SmPC Section 4.5 – Caution when using concomitant medicines with CYP3A4/5 inhibitors SmPC Section 4.8 - Bradycardia is listed as a common (≥1/100 to <1/10) ADR. SmPC Section 4.9 - Recommendations to monitor and treat signs and symptoms following an overdose PL Section 3 – Advice if you take more INTUNIV than you should

	PL Section 4 − Slow heart rate (bradycardia) is a common side effect Prescription only medicine Additional risk minimisation measures: Educational materials for Healthcare professionals

ADR=adverse drug reaction; PL=patient leaflet; SmPC=summary of product characteristics

Important Identified Risk: Syncope	
Evidence for linking the risk to the medicine	Syncope has been reported in clinical trials, post marketing surveillance and scientific literature
Risk factors and risk groups	Patients who have a history of blood pressure dysregulation, arrhythmia, orthostatic hypotension, cardiac and neurologic disorders are at the risk for syncope.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 - Recommendations to conduct a baseline evaluation at pre-treatment screening, a dose titration and ongoing monitoring SmPC Section 4.4 − Recommendations to monitor heart rate and blood pressure. Caution when concomitantly treating patients with antihypertensives or other medicinal products that can reduce blood pressure, heart rate or increase the risk of syncope SmPC Section 4.5 − Caution should be used when treating patients with antihypertensive medicinal products SmPC Section 4.7 − Caution when driving as INTUNIV can cause dizziness and somnolence SmPC Section 4.8 - Syncope/loss of consciousness is listed as an uncommon (≥1/1,000 to <1/100) ADR. PL Section 4 − Feeling faint or loss of consciousness (syncope) is an uncommon side effect Prescription only medicine Additional risk minimisation Additional risk minimisation measures: Educational materials for Healthcare professionals

ADR=adverse drug reaction; PL=patient leaflet; SmPC=summary of product characteristics

Important Identified Risk: Hypotension/Decreased Blood Pressure	
Evidence for linking the risk to the medicine	Hypotension/Decrease blood pressure has been reported in clinical trials, post marketing surveillance and scientific literature
Risk factors and risk groups	Identified risk factors for hypotension include a history of hypotension, bradycardia, heart block or cardiovascular disease, and use of antihypertensives or other drugs that can reduce blood pressure

Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 - Recommendations to conduct a baseline evaluation at pre-treatment screening, a dose titration and ongoing monitoring SmPC Section 4.4 - Recommendations to monitor heart rate and blood pressure. SmPC Section 4.5 – Caution of any addictive effect to INTUNIV. Caution when using concomitant medicines with CYP3A4/5 inhibitors. Caution should be used when treating patients with antihypertensive medicinal products SmPC Section 4.8 - Hypotension and blood pressure decreased are listed as common (≥1/100 to <1/10) ADRs. SmPC Section 4.9 – Recommendations to monitor and treat signs and symptoms following an overdose PL Section 2 – Patients should talk to their doctor or pharmacist if they have low blood pressure or if they are taking any medicine that lowers your blood pressure PL Section 3 – Advice if the patient takes more INTUNIV than they should PL Section 4 – Feeling dizzy (hypotension) is a common side effect Prescription only medicine Additional risk minimisation measures: Educational materials for Healthcare professionals

ADR=adverse drug reaction; PL=patient leaflet; SmPC=summary of product characteristics

Important Identified Risk: Withdrawal Blood Pressure Increase	
Evidence for linking the risk to the medicine	Withdrawal blood pressure increase has been reported in clinical trials, post marketing surveillance and scientific literature for GXR and α2A-AR agonist therapy class.
Risk factors and risk groups	Patients who abruptly discontinue Intuniv treatment without gradual dose downward titration may experience blood pressure and heart rate increase.
Risk minimization measures	Routine risk minimisation measures: Section 4.2 - Recommendation of tapering the dose with stopping INTUNIV SmPC Section 4.4 - Caution as blood pressure could increase with the abrupt withdrawal of INTUNIV. Blood pressure should be monitored when reducing dose or discontinuing SmPC Section 4.8 - Hypertension is listed as a rare ADR, blood pressure increased is listed as an uncommon ADR, and hypertensive encephalopathy is listed as a very rare ADR. PL Section 2 – Talk to your doctor if you have high or low blood pressure. Do not stop taking INTUNIV without talking to a doctor.

	PL Section 3 – Advice if the patient takes more INTUNIV than they should and if the patient stops taking INTUNIV PL Section 4 - Serious withdrawal side effect of high blood pressure after suddenly stopping INTUNIV is very rare Prescription only medicine Additional risk minimisation measures: Educational materials for Healthcare professionals

ADR=adverse drug reaction; PL=patient leaflet; SmPC=summary of product characteristics

Important Identified Risk: Sedative Events	
Evidence for linking the risk to the medicine	Sedative events have been reported in clinical trials, post marketing surveillance and scientific literature
Risk factors and risk groups	Risk factors for sedative events among children and adolescents with ADHD have not been established.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 - Recommendations to conduct a baseline evaluation at pre-treatment screening, a dose titration and ongoing monitoring SmPC Section 4.4 - Recommendation that patients are monitored at the start of treatment and every 3 months during the first year for somnolence. Recommendation that patients should not drink alcohol SmPC Section 4.5 – Caution when administering CNS depressant concomitantly SmPC Section 4.7 – Caution when driving as INTUNIV can cause dizziness and somnolence SmPC Section 4.8 - Somnolence is listed as a very common (≥1/10) ADR, sedation is listed as a common (≥1/100 to <1/10) ADR and hypersomnia is listed as a rare (≥ 1/10,000 to < 1/1,000) ADR. PL Section 2 – Patients should tell their doctor or pharmacist if they are taking any medicine that makes them sleepy (sedative) PL Section 4 – Feeling sleepy (somnolence) and feeling tired (fatigue) is very common Prescription only medicine Additional risk minimisation measures: Educational materials for Healthcare professionals

ADR=adverse drug reaction; PL=patient leaflet; SmPC=summary of product characteristics

Important Identified Risk: Weight Increase	
Evidence for linking the risk to the medicine	Weight increase has been reported in clinical trials, post-marketing and literature.

Risk factors and risk groups	Patients who are overweight at baseline, patients who are inactive and/or increase of food intake, who have metabolic disorders may be at risk for the risk of weight increase.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 - Recommendations to conduct a baseline evaluation at pre-treatment screening, dose adjustments and ongoing weight monitoring SmPC Section 4.4 – Recommendations to monitor weight SmPC Section 4.8 - Weight increase is listed as a common (≥1/100 to <1/10) ADR PL Section 2 – Patients should be informed that INTUNIV may affect their weight and their doctor will check their weight throughout their treatment PL Section 3 – The patients' doctor will make dose adjustments based on their body weight PL Section 4 – Weight gain is a common side effect Prescription only medicine Additional risk minimisation measures: Educational materials for Healthcare professionals

ADR=adverse drug reaction; PL=patient leaflet; SmPC=summary of product characteristics

Important Potential Risk: QT prolongation	
Evidence for linking the risk to the medicine	QT prolongation has been reported in clinical trials and post-marketing
Risk factors and risk groups	Risk factors for that have been identified in children include female gender, age, prior syncopal history, QT-interval duration, and genetic/familial factors (Goldenberg et al. 2008). Most research in this area has focused upon the risk factors for serious cardiac events following diagnosis of LQTS.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 – Posology and method of administration SmPC Section 4.4 - Special warnings and precautions for use SmPC Section 4.5 - Caution of any addictive effect to INTUNIV. INTUNIV with QT prolonging medicinal products is generally not recommended Prescription only medicine Additional risk minimisation measures: No risk minimisation measures.

LQTS=long QT syndrome; SmPC=summary of product characteristics

Important Potential Risk: Off-label Use	
Evidence for linking the risk to the medicine	Off label use has been seen in post marketing surveillance reports
Risk factors and risk groups	All patients under age 6 years of age, and above 17 years of age.
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 – It is not recommended to use INTUNIV in Adults, elderly patients or children under 6 years PL Section 2 – This medicine should not be used in children under 6 years of age and adults 18 years and over Prescription only medicine Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Drug utilisation study See section II.C of this summary for an overview of the post-authorisation development plan.

PL=patient leaflet; SmPC=summary of product characteristics

Missing Information: Use in pregnant or breastfeeding women	
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.6 – INTUNIV is not recommended during pregnancy. A decision must be made whether to discontinue breast-feeding or to discontinue and/or abstain from Intuniv therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman PL Section 2 – Patients that are pregnant or breastfeeding, think they may be pregnant or planning on having a baby, should ask their doctor or pharmacist for advice. Patients should not take this medicine if they are pregnant or breastfeeding. Prescription only medicine Additional risk minimisation measures: No risk minimisation measures.

PL=patient leaflet; m2= square meter; SmPC=summary of product characteristics.

Missing Information: Use in patients with hepatic or renal impairment	
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 – Dose reduction may be required for patients with hepatic and renal impairment.

Missing Information: Use in patients with hepatic or renal impairment	
	Prescription only medicine Additional risk minimisation measures: No risk minimisation measures.

PL=patient leaflet; SmPC=summary of product characteristics.

Missing Information: Long term safety (neurocognition in particular but also effects on growth, sexual maturation)	
Risk minimization measures	Routine risk minimisation measures: SmPC Section 4.2 – Dose reduction may be required for patients with hepatic and renal impairment. Prescription only medicine Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: SPD503-401

SmPC=summary of product characteristics.

II.C. Post-authorisation development plan

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

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

ADHD=attention-deficit/hyperactivity disorder; CANTAB=Cambridge Neuropsychological Test Automated Battery.

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

Study name	Purpose of the study
Drug utilisation study of INTUNIV (guanfacine extended release) in the European Union	Shire Pharmaceuticals plans to launch INTUNIV in Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Norway, Spain, Sweden and UK from January 2016 onwards. Shire Pharmaceuticals will conduct a drug utilization study for up to five years as part of the risk management plan for INTUNIV in Europe.

ADHD=attention-deficit/hyperactivity disorder.