EMA/530486/2015

Summary of the risk management plan (RMP) for Intuniv (guanfacine)

This is a summary of the risk management plan (RMP) for Intuniv, which details the measures to be taken in order to ensure that Intuniv is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Intuniv, which can be found on Intuniv's EPAR page.

Overview of disease epidemiology

Intuniv is a medicine used to treat attention-deficit hyperactivity disorder (ADHD), a behavioural disorder that involves short attention span and inability to concentrate, restlessness and constant talking and movement, and impulsive behaviour. ADHD is one of the most common behavioural disorders affecting children and adolescents. ADHD starts during childhood and may continue into adulthood. Individuals with untreated ADHD have higher risk for cigarette smoking and alcohol and substance abuse. Young people with ADHD are also at a higher risk for suicidal behaviour. ADHD is associated with other mental disorders such as anxiety, depression and learning disability. It is estimated that 5 percent of children aged 6-17 years have ADHD in Europe.

Summary of treatment benefits

Several studies have shown Intuniv improving ADHD symptom scores (ADHD-RS-IV) in children and adolescents.

In a study of 337 children aged 6 to 17 years, the reduction in ADHD symptoms with Intuniv treatment after 10 to 13 weeks was 24 points compared with a reduction of 15 points seen with placebo (a dummy treatment) and 19 points seen with atomoxetine (an ADHD medicine). In another study of 312 adolescents aged 13 to 17, the reduction in ADHD scores at 13 weeks was 25 points with Intuniv and 19 points with placebo. Two other short-term studies involving 631 patients also showed Intuniv at various doses improving ADHD scores more than placebo.

Intuniv was also evaluated in terms of treatment failures (based either on worsening of ADHD symptoms or patients stopping treatment). In a long-term maintenance study in 301 children and adolescents aged 6 to 17 years treatment failures occurred in 49% of patients taking Intuniv compared with 65% of those taking placebo.

Unknowns relating to treatment benefits

There is little or no information on the use of this medicine in pregnant women, children with liver or kidney disease, or children under 6 years of age.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Slow heartbeat (bradycardia)	In studies to license the medicine most cases of slow heartbeat did not require any treatment and resolved.	Heart rate and blood pressure should be measured before starting treatment with Intuniv and then every week while the dose is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year.
Fainting (syncope)	In clinical studies most cases of fainting did not require treatment and resolved. However, fainting suddenly can result in a fall and injury.	Heart rate and blood pressure should be measured before starting treatment with Intuniv and then every week while the dose is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year.
Low blood pressure (hypotension/decreased blood pressure)	In clinical studies most cases of low blood pressure did not require any treatment and resolved.	Heart rate and blood pressure should be measured before starting treatment with Intuniv and then every week while the dose is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year.
High blood pressure when the medicine is stopped suddenly (withdrawal blood pressure increase)	Stopping this medicine suddenly can cause the blood pressure to increase, a so-called withdrawal effect. The increase is generally not serious but there is a risk for a more severe increase in blood pressure if a patient has had high blood pressure in the past.	When stopping treatment with Intuniv, it is recommended that the dose is reduced gradually to minimise the likelihood of withdrawal effects. It is important that patients do not stop taking this medicine without first talking to the doctor because the ADHD may come back and blood pressure and heart rate may increase.
Drowsiness possibly with slowing down of breathing and heart rate (sedative events)	In clinical studies most cases of sleepiness did not require any treatment and resolved. However, sleepiness can be severe and may result in an accident and injury.	Patients should be closely monitored weekly while the dose of Intuniv is being adjusted. When the right dose has been established, heart rate and blood pressure should be measured at least every 3 months for the first year and then at least twice a year.
Weight increase	In long-term clinical studies, the body mass index (BMI) of a small number of patients increased 12 months after starting this medicine	As part of routine monitoring height, weight and BMI should be monitored. It is important for the patient to tell the doctor or pharmacist about any problem with weight

Risk	What is known	Preventability
	compared to when they began receiving it. BMI indicates if a person is of healthy weight; an increase in BMI suggests that the person is putting on extra weight.	before taking this medicine.

Important potential risks

Risk	What is known
Disease of the heart valves (cardiac valvulopathy)	Intuniv binds to 5HT-2B receptors, which are known to be involved the development of cardiac valvulopathy.No reports of cardiac valvulopathy have been seen in clinical studies with Intuniv or after marketing.
Alteration of the electrical activity of the heart (QT interval prolongation)	In clinical studies, cases of QT interval prolongation were mostly moderate in severity and resolved. There were no serious cases.
Use of the medicine in unapproved populations (off-label use)	This medicine has not been studied in children under age 6 years, adults and the elderly, and is not approved for use in these populations.
Blood sugar disorder (blood glucose disorder)	In clinical studies, most cases of blood glucose disorder were mild in severity.

Missing information

Risk	What is known
Use during pregnancy or breast feeding	There is no information on the use of this medicine in pregnant or breastfeeding women.
Use in patients with liver or kidney disease	There is no information on the use of this medicine in patients with liver or kidney disease.
Long-term safety especially effects on growth, sexual maturation and mental processes such as thinking, learning and memory in particular parts of the brain (neurocognition)	There is limited information about the effects of this medicine with long-term use, especially on how it could affect growth, sexual maturation or neurocognition (see section on post-authorisation development plan)
Drug interactions	Studies to further evaluate potential drug interactions are planned (see section on post-authorisation development plan).

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Intuniv can be found on Intuniv's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Intuniv's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Bradycardia, syncope, hypotension/decreased blood pressure, withdrawal blood pressure increase, sedative events, and weight increase

Risk minimisation measure: Educational material for healthcare professionals
Objective and rationale: to address the risks of bradycardia, syncope, hypotension/decreased blood pressure, withdrawal blood pressure increase, sedative events, and weight increase.
Description: The educational materials are to remind healthcare professionals about the screening to be performed before deciding if the patient is a candidate to receive Intuniv and on the examinations to be performed periodically during treatment.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Drug utilisation study of Intuniv (guanfacine extended release) in the European Union	Primary objective: To characterise patients who are prescribed guanfacine To describe prescribing patterns of guanfacine among physicians Secondary objective: To measure the effectiveness of the	Off-label use. Effectiveness of the educational materials for healthcare professionals	Planned	Annual reports planned 1st year after approval (to coincide with PSUR)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	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 Guanfacine Hydrochloride Extended Release for European Children and Adolescents Aged 6-17 Years with Attention- Deficit/Hyperactivity Disorder (ADHD) who participated in study SPD503-315 or SPD503-316	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 Long-term efficacy	Started	Submission of final study report: 31 Mar 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	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: To further characterise the risks of hypotension, syncope, sedative events, weight increase, bradycardia growth, sexual maturation and QT	Long-term safety (neurocognition in particular, but also effects on growth, sexual maturation)	Planned	Submission of protocol: 31 July 2016 Submission of final study report: 31 Jan 2022

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	prolongation.			
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 drug-drug interactions)	To identify the transporter involved in hepatic uptake	Potential drug interaction	Planned	Submission of final results: March 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. 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	To identify if guanfancine is an inhibitor of CYP enzymes and drug transporters	Potential drug interaction	Planned	Submission of final results: Jan 2016

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
of TDI); Transporters BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3				
V7400M-SPD503: The MAH should re-perform the CYP induction study in line with the current EMA guideline on drug-drug interaction	To identify if guanfancine can induce CYP enzymes	Potential drug interactions	Planned	Submission of final results: Nov 2015
The marketing authorisation holder to 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.	To evaluate the pharmacological activity of 3-hydroxy guanfacine sulfate	Efficacy and potential interaction	Planned	Metabolite synthesis completed: Nov 2015. Evaluation of pharmacological activity: Feb 2016

Studies which are a condition of the marketing authorisation

Study SHP503-401 is a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 08-2015.