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Public Risk Management Plan (RMP) Summary

REVATIO (Sildenafil)

Film coated tablets & Solution for Injection

Disclaimer:

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 risks as well as to prevent or minimise them.
The RMP summary of Revatio 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 Revatio in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Viatris Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Revatio.

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Summary of risk management plan for Revatio

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

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

The Medicine and What It Is Used For

Revatio is authorised for treatment of adult patients with pulmonary arterial hypertension (PAH) classified as World Health Organization (WHO) functional class II and III, to improve exercise capacity. It contains sildenafil citrate as the active substance, and it is given by oral route of administration or as a solution for injection.

Further information about the evaluation of Revatio's benefits can be found in Revatio's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/revatio.

Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Revatio, together with measures to minimise such risks and the proposed studies for learning more about Revatio'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 addition to these measures, information about adverse events 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 Revatio is not yet available, it is listed under 'missing information' below.

List of Important Risks and Missing Information

Important risks of Revatio 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 Revatio. 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	• Vaso-occlusive crisis in patients with sickle cell disease • Increased relative mortality in the paediatric population • Bleeding events (excluding epistaxis)
Important potential risks	• Non-arteritic anterior ischaemic optic neuropathy (NAION) • Pulmonary haemorrhage in paediatric patients
Missing information	• Long-term ocular safety • Safety in pregnancy • Long-term mortality

Summary of Important Risks

Important Identified Risk: Vaso-occlusive Crisis in Patients with Sickle Cell Disease

Evidence for linking the risk to the medicine	The rationale for the addition of risk of vaso-occlusive crisis in patients with sickle cell anaemia was based on results of the Walk PHaSST (treatment of Pulmonary Hypertension and Sickle cell disease with Sildenafil Therapy) Study. This study was a multicentre, placebo-controlled, double-blind, 16-week trial evaluating the safety and efficacy of oral sildenafil for the treatment of Doppler-defined PAH (tricuspid regurgitant jet velocity [TRV] $\geqslant$2.7 m/s) in adults and children (aged >12 years) with sickle cell anaemia. The planned sample size was 132 randomised subjects with an 80% – 90% power to detect 40 metres treatment difference on the change in 6-minute walk distance (6MWD) from baseline. The Walk PHaSST study was sponsored by the US National Heart, Lung, and Blood Institute (NHLBI), and the MAH's participation was limited to the provision of the active compound sildenafil citrate. This study was terminated early by the NHLBI based on the Data Safety

	Monitoring Board's recommendation because of more serious adverse events of vaso-occlusive crisis in the sildenafil (PAH)-treated arm compared with placebo. Seventy-four subjects were randomised, 37 in each arm. In the sildenafil (PAH) group, 13 individuals (35%) reported 18 vasoocclusive crises, compared with 5 individuals (14%) with 8 crises in the placebo group, a difference that was considered statistically significant (p=0.029). A review of clinical studies reported in the literature has failed to identify other reports of vaso-occlusive crisis occurring when patients with sickle cell anaemia have been treated with sildenafil (PAH), or identify a definitive biologically plausible mechanism, by which sildenafil (PAH) might increase the risk of vaso-occlusive crisis in subjects with sickle cell anaemia. Published reports have suggested a potential role for sildenafil in the treatment of patients with PAH associated with sickle cell disease. In these uncontrolled studies, sildenafil (PAH) appeared to be well tolerated and improved functional capacity and decreased estimated right ventricular systolic pressures. The results of the Walk PHaSST study are inconsistent with these previously published reports. Analysis of the final study cohort suggested there was no treatment effect between sildenafil and placebo on 6MWD (p=0.703), TRV (p=0.503), or NT-proBNP (p=0.410). However, the final analysed study cohort (N = 74) was much smaller than the pre-specified sample size (N = 132) based on the power calculation put forth in the original protocol. Several confounders were identified in the Walk PHaSST study: • Baseline imbalances in the study treatment groups may have predisposed to the occurrence of vaso-occlusive crisis in the sildenafil (PAH) group. Patients in the sildenafil (PAH) group appeared to have worse disease at baseline as evidenced by lower haemoglobin and significantly higher creatinine and higher NT-pro BNP. • Not all patients were on maximized sickle cell disease specific therapy prior to initiating study treatment, for example hydroxyurea. • Hospitalization rates prior to enrolment in Walk-PHaSST were not collected and therefore it was not possible to evaluate the bias due to previous vaso-occlusive crisis. This information is critical to understanding the study data as patients hospitalized for sickle cell disease have higher risk of re-hospitalization. The absence of this information represents a major challenge to the interpretation of the Walk PHaSST data.Concomitant medical events occurring during the study may have also been a factor in the incidence of vaso-occlusive crisis. A review of these events demonstrates that 9/13 (~70%) of patients receiving sildenafil (PAH), compared to 2/5 (40%) in the placebo group experienced a concomitant AE which may have predisposed to a vaso-occlusive crisis.
Risk factors and risk groups	Patients with sickle cell disease.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4, *Special warnings and precautions for use* PL Section 2, *What you need to know before you take Revatio* Additional risk minimisation measures: None.

Important Identified Risk: Increased Relative Mortality in the Paediatric Population

Evidence for linking the risk to the medicine	Data from Study A1481156, the long-term, open-label extension to the sildenafil (PAH) paediatric pivotal study (A1481131), provides evidence which suggests an increased risk of mortality in paediatric patients treated with high doses of sildenafil (PAH), compared to low doses, as defined in the study. The number (%) of deaths was 5/55 (9.1%), 13/74 (17.6%) and 24/100 (24%) in sildenafil low, medium and high dose groups, respectively, in Study A1481156 (see Table below)

Summary of Deaths n (%) by Weight Group and Sildenafil (PAH) Dose Group

Body Weight (kg) [a]	Sildenafil (PAH) Low Dose (N = 55)	Sildenafil (PAH) Medium Dose (N = 74)	Sildenafil (PAH) High Dose (N = 100)
≥8–20	NA	N = 20	N = 44
	-	n = 1 (5.0%)	n = 6 (13.6%)
>20–45	N = 40	N = 40	N = 41
	n = 3 (7.5%)	n = 10 (25.0%)	n = 15 (36.6%)
>45	N = 15	N = 14	N = 15
	n = 2 (13.3%)	n = 2 (14.3%)	n = 3 (20.0%)
Total	N = 55	N = 74	N = 100
	n = 5 (9.1%)	n = 13 (17.6%)	n = 24 (24.0%)

Produced by summation of sildenafil dose group with placebo + sildenafil (PAH) dose group.
NA: not applicable
[a] For placebo subjects in Study A1481131, weights collected at Week 16 were used. Subject 11612 randomly assigned to sildenafil (PAH) medium dose in Study A1481131 had a baseline weight of 44.6 kg, but was incorrectly assigned to the >45 kg weight group for randomization stratification. In this table, the subject is correctly assigned to the weight group of >20-45 kg

The Kaplan-Meier survival estimates for the low, medium, and high randomised dose groups at 3 years were 94%, 93%, and 88%, respectively. These survival rates are substantially higher than reported in children with PAH prior to the availability of targeted PAH therapies. The 1, 3, and 5 year survival rates of paediatric PAH patients prior to the availability of targeted therapy have been reported as a range of 37%-66%, 29%-52%, and 29%-35%, respectively.

Across all dose groups, the probability of survival at Year 1, Year 2 and Year 3 relative to the start of sildenafil (PAH) ranged from 99%-100%, 93%-96% and 88%-94%, respectively. Kaplan-Meier estimates are likely to be over estimates, as those subjects lost to follow-up may have a poorer survival prognosis than those subjects whose survival status was known.

Forty-two (42) deaths were reported in Study A1481156. Of these, 37 deaths were reported as serious adverse events and none was considered to be treatment-related by the investigators. An additional 5 deaths were reported as part of the survival follow-up. Examination of the baseline characteristics of the subjects who died revealed that the majority of subjects had primary PAH, more commonly were Functional Class III or IV, and generally had more severe haemodynamic abnormalities at baseline.

Risk factors and risk groups	Paediatric patients aged between 1 and 17 years.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, *Posology and method of administration* SmPC Section 4.4, *Special warnings and precautions for use* Section 5.1, *Pharmacodynamic properties* PL Section 3, *How to take Revatio* Additional risk minimisation measures: None.

Important Identified Risk: Bleeding Events (Excluding Epistaxis)

Evidence for linking the risk to the medicine	Bleeding events (excluding epistaxis) have been report in sildenafil (PAH) clinical trials and in the post-marketing setting.
Risk factors and risk groups	Patients with bleeding disorders, active peptic ulceration or patients using a vitamin K antagonist.
Risk minimisation measures	Routine Risk Minimisation measures: SmPC Section 4.4, *Special warnings and precautions for use* Section 4.8, *Undesirable effects* PL Section 2, *What you need to know before you take Revatio* *PL Section 4, Possible side effects* Additional risk minimisation measures: None.

Important Potential Risk: Non-arteritic Anterior Ischaemic Optic Neuropathy (NAION)

Evidence for linking the risk to the medicine	*Non-interventional Study (A1481259)* An observational non-interventional, case-crossover Study (A1481259) was conducted to examine whether as-needed use of PDE5 inhibitors for treatment of erectile dysfunction, as a class (including Viagra, vardenafil, or tadalafil) triggers the onset of acute NAION within a pharmacokinetically-defined time period (approximately 5 half-lives) following drug ingestion. A total of 673 subjects who met the potential acute NAION case criteria were enrolled across 66 sites. Seventy-six (76) subjects were exposed and 597 subjects were unexposed to PDE5

	inhibitor in the 60 day period prior to the onset of NAION symptoms. In the primary analysis, the PDE5 inhibitor exposure status of the day preceding NAION symptom onset (the case window) was compared with the PDE5 inhibitor exposure status of the 29 days preceding the case window (the 29 control windows). For the 43 Definite NAION cases, the estimated odds ratio (OR) was 2.15 and the 95% CI was (1.06, 4.34) based on conditional logistic regression. This OR suggests a 2.15 fold increase in the odds of acute NAION onset within 5 half-lives of PDE5 inhibitor use as compared with PDE5 inhibitor use prior to the pharmacokinetically-defined time window but within the 30 days prior to onset. For the Definite and Possible NAION cases combined, the OR was 2.36 (95% CI 1.33, 4.19). The primary analysis of Definite NAION cases suggests an approximately 2-fold increased risk of NAION within 5 half-lives of PDE5 inhibitor use; given that the outcome is rare, the OR may be interpreted as an estimate of the relative risk. To put these findings into context, the absolute risk (ie, risk difference) was estimated by applying the estimated OR of 2.36 based on subjects adjudicated as Definite or Possible NAION cases to an estimate of the background annual risk of NAION and accounting for the average proportion of days in a given year that a PDE5 inhibitor user is exposed. Using conservative assumptions, PDE5 inhibitor use is estimated to add 3 to 8 cases per 100,000 males 50 years and older per year. *Other population-based observational studies* The sildenafil Prescription Event Monitoring (PEM) post-marketing study of more than 28,000 patients receiving a UK National Health Service prescription for the drug was independently conducted by the Drug Safety Research Unit (DSRU) at the University of Southampton between 1998 and 2001. Two different cohorts comprise the study population; the first cohort of 5601 patients was observed for a mean of 6 months and the second cohort of 22,473 patients was observed for a mean of almost 18 months. Only one case of NAION in the second cohort, was reported to the DSRU over the course of the study. Based on the approximately 35,569 person-years of observation during Cohorts I and II, the unadjusted incidence of NAION in the PEM study is 2.8 per 100,000 person-years, and is consistent with the rate obtained by Johnson (2.5 per 100,000 men per year). The International Men's Health Study (IMHS), a prospective cohort study conducted by the MAH between 2001 and 2004 of 3813 men (mean age=57 years, range: 18 – 100) receiving a Viagra prescription in Germany, France, Spain, and Sweden, identified no cases of NAION during 2935 patient-years of follow-up. A further search of the MAH safety database identified two cases from the IMHS that reported "optic nerve disorder": one mentioned "anterior optic nerve ischaemia" in a 52-year-old man with prior loss of an eye (reason for the loss unspecified); the other was reported as "optic nerve impairment" in a 57-year-old man. In addition to age, both cases described other significant predisposing factors such as hyperlipidemia, hypertension, prior myocardial infarction, and prior cardiac catheterization, and it is unknown when and if sildenafil was used around the time of their optic nerve event onset.

	Post-Marketing Experience NAION has been reported rarely in the post-marketing setting with the use of all PDE5 inhibitors, including sildenafil.
Risk factors and risk groups	Although the aetiology of NAION is unknown, many of its risk factors are similar to those for erectile dysfunction such as ischaemic heart disease, hypertension, hypercholesterolemia, diabetes, and increased age. Other potential risk factors for NAION are sleep apnea, hyperhomocystinemia, the presence of a disc- at-risk, cataract extraction and intraocular lens surgery, disorders of blood coagulation and specifically thrombotic tendency. A growing body of evidence suggests an association between thrombophilic risk factors and NAION, particularly when other associated microvascular risk factors (hypertension, diabetes, hyperlipidemia, smoking) cannot specifically be identified. In particular, Glueck et al (2004) demonstrated an association between NAION and homozygosity for the C677T methylenetetrahydropholate reductase mutation. Patients with NAION were also more likely to carry other genetic mutations associated with thrombophilia. Women with NAION were more likely to have estrogen-induced thrombophilia than were controls. Alterations of the immune system may be a risk factor that NAION and pulmonary PAH share. Antiphospholipid syndrome frequently presents with arterial and/or venous thrombosis in association with laboratory evidence of persistent lupus anticoagulant, and the thrombotic risk in these patients is increased by additional risk factors such as the factor V Leiden mutation Johnson reported that NAION typically affects those in the 6th decade of life with the median occurrence at 62 years, but incidence can range from 40-80+ years. In addition, cases of NAION in women and at younger age have been reported linked to conditions associated with alteration of the immune system (Reiter's syndrome), antiphospholipid syndrome. Other ophthalmologic risk factors have been identified; patients who have experienced an episode of NAION in one eye are at higher risk of having it occur in the opposite eye, as well as those who have had cataract extraction, intraocular lens surgery, or who have a 'disc at risk'. Case reports of NAION have also been reported with medications, including systemic interferon alpha therapy, influenza vaccination, amiodarone, sumatriptan, and the use of some amphetamine derivatives such as phentermine. However, the evidence for a causal relationship between these drugs and NAION is inadequate, and the potential mechanism(s) involved for such disparate pharmacologic classes are still unknown.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3, *Contraindications* SmPC Section 4.4, *Special warnings and precautions for use* SmPC Section 4.8 *Undesirable effects* PL Section 2, *What you need to know before you take Revatio* PL Section 4, *Possible side effects* Additional risk minimisation measures: None.

Important Potential Risk: Pulmonary Haemorrhage in Paediatric Patients

Evidence for linking the risk to the medicine	A publication in 2014 described pulmonary haemorrhage in two extremely premature babies (<30 weeks gestational age) treated off-label with sildenafil for respiratory failure and patent ductus arteriosus. Both cases originated from a small retrospective study of 6 children treated at the same hospital in Austria. The two children developed pulmonary haemorrhage 19 and 66 hours after the start of sildenafil treatment. The conclusion of the publication stated that sildenafil treatment seems effective in improving severe pulmonary hypertension and haemodynamic instability in extremely preterm infants with refractory pulmonary hypertension, but that pulmonary haemorrhage may represent a distinct adverse effect of sildenafil treatment in these patients, presumably due to the sudden reversal of ductal shunt. Accordingly, sildenafil should be restricted to most severe and refractory cases in this population. Pulmonary haemorrhage in paediatric patients has been added as an important potential risk at the request of the EMA PRAC, following its assessment of the MAH's comprehensive safety evaluation of the preclinical data, published medical literature, clinical safety and post-marketing safety data involving the topic of pulmonary haemorrhage in paediatric patients receiving sildenafil for PAH. The EMA PRAC reviewed the data and agreed with the MAH's conclusion that there was at present insufficient evidence to establish a causal relationship between pulmonary haemorrhage and sildenafil in paediatric patients; however, in consideration of the seriousness and life-threatening nature of pulmonary haemorrhage in premature children, the PRAC final recommendation (May 2015) was to include pulmonary haemorrhage in the RMP as an important potential risk at the next regulatory opportunity and closely monitor this potential risk in future period safety update reports (PSURs). Of note, no SmPC revisions were requested by the EMA PRAC with regards to pulmonary haemorrhage.
Risk factors and risk groups	Pulmonary haemorrhage may develop more likely in preterm newborns with more incident BPD; in PAH patients treated with inhaled nitric oxide (NO), especially concomitant with sildenafil; in infants with low birth weight and premature gestational age, respiratory distress syndrome, infection, male gender and the presence of patent ductus arteriosus.
Risk minimisation measures	No risk minimisation measures.

Missing Information: Long-term Ocular Safety

Risk minimisation measures	No risk minimisation measures.

Missing Information: Safety in Pregnancy

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 Fertility, pregnancy and lactation PL Section 2, What you need to know before you take Revatio Additional risk minimisation measures: None.

Missing Information: Long-term Mortality

Risk minimisation measures	No risk minimisation measures

Post-Authorisation Development Plan

Studies which are Conditions of the Marketing Authorisation

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

Other Studies in Post-Authorisation Development Plan

Study A1481324

Purpose of the study: To test for the non-inferiority of sildenafil 80 mg versus 5 mg for mortality; i.e., mortality rate with the 80 mg dose is no worse than double the mortality rate for the 5 mg dose.

Study A1481319

Purpose of the study: To obtain the information on dosage and administration, safety, and effectiveness of sildenafil (PAH) when it is administered for a long period of time (1 year) under the actual use by paediatric patients treated with sildenafil (PAH) in Japan.