RAPISCAN (REGADENOSON)

Generic name: Rapiscan
Active substance: Regadenoson
Dosage levels: One level, no adjustment needed
Single injection of 400 micrograms regadenoson (5 ml)
Galenic form: Solution for injection

SUMMARY OF RISK MANAGEMENT PLAN
Version 12

Date of report: November 2020

Marketing Authorisation Holder:
GE Healthcare AS, P.O.Box 4220 Nydalen, N-0401 Oslo, Norway

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 minimize them.

The RMP summary of Rapiscan 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" 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 Rapiscan in Switzerland is the "Arzneimittelinformation"
(see www. Swissmedicinfo.ch) approved and authorized by Swissmedic. GE Healthcare AS is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Rapiscan.

1. Summary of the risk management plan (RMP) for Rapiscan (regadenoson)

This is a summary of the risk management plan (RMP) for Rapiscan, which details the measures to be taken in order to ensure that Rapiscan is used as safely as possible. The reference document which is valid and relevant for the effective and safe use of Rapiscan in Switzerland is the "**Arzneimittelinformation**" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

All medicines have a Summary of Product Characteristics (SPC) that provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Rapiscan (regadenoson) can be found in the Rapiscan's EPAR page.

A Direct Healthcare Professional Communication (DHPC) was issued to communicate the identified risk of cerebrovascular accident and the risk of aminophylline prolongation of regadenoson-induced seizure and the relevant clinical actions to minimize these occurrences

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 in Rapiscan's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

2. Table of current safety concerns

Table 1 below presents current safety concerns identified for Rapiscan in EU Risk Management plan. This is only applicable in EEA and some other countries where Regadenoson is additionally approved for the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurement are not anticipated. This FFR indication however has not been submitted in Switzerland up to now, and Table 2 below summarises the safety concerns applicable for Rapiscan in Switzerland.

Table 1 List of safety concerns identified in Rapiscan EU RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Important missing information	Safety of repeated use in fractional flow reserve (FFR) indication

Table 2 List of safety concerns identified in Rapiscan RMP in Switzerland

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Important missing information	None

3. Summary of safety concerns removed from the list of safety concerns

There were no new safety concerns identified since the previous approved Rapiscan RMP. In this renewal of the RMP, the safety profile has been updated. The following risks previously classified as important identified and important potential risks were reclassified and removed from the list of safety concerns, see Table 3. These are known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting.

Table 3 Summary of safety concerns removed from the list of safety concerns

Reclassified Risks	
Important identified risks	SA/AV nodal block
	Myocardial ischemia
	Hypotension
	Hypersensitivity
	Seizures
	Prolongation of regadenoson-induced seizures following administration of aminophylline
	Worsening/recurrence of atrial fibrillation
	Elevated blood pressure and hypertensive crisis
	Cerebrovascular accident (CVA, stroke)
	Respiratory compromise (bronchoconstriction and respiratory arrest)
Important potential risks	Off-label use involving exercise
Missing information	Safety in children
	Safety in pregnancy
	Safety in lactation
	Safety in patients with prolonged QT syndrome

4. Summary of Risk Minimisation measures

Table 4 below presents a summary of the pharmacovigilance activities and risk minimisation activities with regard to use of Rapiscan in EEA. No risk minimisation activities are applicable in Switzerland as FFR indication is not approved. There are no other safety concerns for Rapiscan in Switzerland which require risk minimisation measures.

Table 4 Summary table of pharmacovigilance activities and risk management activities for safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information Repeat use in FFR indication	Routine risk minimisation measures in EU: - EU SmPC sections 4.2, 5.1 and 5.2, - EU SmPC section 4.2 where it is advised not to administered Rapiscan more than twice, and no less than10 minutes apart for FFR, during any 24-hour period - EU SmPC section 4.2 and 5.1 where it is advised to administer as a rapid 10 second injection into a peripheral vein, using a 22 gauge or larger catheter or needle for FFR - Rapiscan is prescription only medicine. Routine risk minimisation measures in Switzerland: Not applicable Additional risk minimisation measures: - None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection in EU: - targeted follow-up questionnaire. Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection in Switzerland: - Not applicable Additional pharmacovigilance activities: - none.

5. Elements for a Public Summary in EEA

The section presents overview of disease epidemiology, summary of treatment benefits and summary of risk minimization measures with regard to important missing information Repeat use in FFR indication. This is only applicable in EEA and some other countries where Regadenoson is additionally approved for the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurement are not anticipated. This FFR indication however has not been submitted in Switzerland up to now, therefore this section is not applicable in Switzerland.

5.1. Overview of disease epidemiology

Coronary artery disease (CAD) is a progressive disease that can cause blockage of the vessels that supply blood and nutrition to the heart. This process results in myocardial ischemia, which can cause chest pain, angina and myocardial infarction (or “heart attack”). Approximately 3 million people in the EU are affected by CAD, who requires diagnostic tests to determine the presence, location and severity of their disease.

Myocardial perfusion imaging (MPI) is a non-invasive diagnostic procedure that determines the functional consequence of an obstruction resulting from coronary artery disease. When combined

with single-photon emission computed tomography, MPI facilitates the diagnosis of coronary artery disease, assesses the risk of future cardiac events, and guides clinical decisions regarding medical treatment, revascularisation or urgent intervention.

Fractional flow reserve (FFR) is a technique used in coronary catheterization to measure pressure differences across a coronary artery stenosis (narrowing, usually due to plaque build-up) to determine the likelihood that the stenosis impedes oxygen delivery to the heart muscle (myocardial ischemia).

Regadenoson is a selective coronary vasodilator for use as a pharmacological stress agent for radionuclide MPI in adult patients unable to undergo adequate exercise stress and for the measurement of FFR of coronary artery stenosis of unknown functional significance in adult patients

5.2. Summary of treatment benefits

A total of 3,142 patients have been dosed to regadenoson in thirteen clinical trials: 1,684 of these patients were enrolled in the Phase 3 studies (ADVANCE MPI 1 and 2 studies and 3606-CL-3002) in the target population of patients with a clinical indication for pharmacological stress radionuclide myocardial perfusion imaging, and 1,006 patients were enrolled in the Phase 4 studies examining the safety and tolerance of regadenoson in subjects with asthma or chronic obstructive pulmonary disease (COPD; study 3606-CL-3001) or renal impairment (study 3606-CL-3010). The pivotal Phase 3 trials tested the safety and efficacy of regadenoson compared to adenosine in patients clinically indicated to undergo a pharmacological stress myocardial perfusion imaging study. The ADVANCE MPI 1 and ADVANCE MPI 2 studies, individually and combined, demonstrated that Rapiscan is effective in assessing the extent of reversible myocardial perfusion abnormalities, which is used to diagnose coronary artery disease. Although the knowledge of the safety of regadenoson continues to increase with its use in clinical practice, in the phase 3 trials some adverse reactions appeared less frequently with regadenoson than adenosine (chest pain, flushing and ‘throat neck and jaw pain’) and some adverse reactions (headache) were higher with regadenoson than adenosine.

FFR measurements obtained with regadenoson are nearly identical to the pharmacological stress agent adenosine. Although adenosine has been established clinically as the gold standard for the measurement of FFR to guide percutaneous coronary intervention, adenosine is not approved for this use. Although the use of FFR to guide coronary intervention has been demonstrated to improve patient outcomes (death, myocardial infarction, and urgent revascularization) and health resource utilization {Fearon 2010}, there is no pharmacological stress agent approved for use to cause maximum hyperaemia during the measurement of FFR. Thus, a significant unmet medical need exists for a regadenoson to be indicated for the measurement of FFR.

Regadenoson provides a more convenient mode of administration, and a less error-prone dosing alternative to the other vasodilator stress agents currently used in radionuclide MPI procedures and for the measurement of FFR, and may prove to be better tolerated than adenosine.

5.3. Unknowns relating to treatment benefits

Insufficient information exists using Rapiscan for repeated use in FFR

6. Summary of safety concerns

6.1. Details of important identified risks, important potential risks, and missing information

6.1.1. Important identified risks

No important identified risks are identified for regadenoson.

6.1.2. Important potential risks

No important potential risks are identified for regadenoson.

6.1.3. Missing information

Safety of repeated use in FFR indication (applicable in EEA only).

The safety of repeated dosing has been studied in healthy volunteers [Townsend et al. 2017] and in patients with CAD [van Nunen et al. 2015]. In these studies, 36+88=124 individuals received more than one dose of regadenoson. The efficacy and safety of repeated dosing of regadenoson were studied in an Investigator Initiated Trial which included 100 adult patients with a broad range of coronary stenosis severity (30 to 90%) by visual assessment of coronary angiograms [Clinical Study Report Regadenoson 2016]. Results were well balanced between treatment groups. The anticipated risk/consequence of the missing information is expected to be low.

6.2. Routine Risk Minimisation Measures

The routine pharmacovigilance activities for Rapiscan include a request for additional information about the safety of repeated use in fractional flow reserve (FFR) measurement by using a targeted follow-up questionnaire. The objective is to ensure that all reports concerning safety are carefully assessed so that additional measures can be introduced, if justified by emerging data.

This is only applicable in EEA and some other countries where Regadenoson is additionally approved for the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurement are not anticipated. This FFR indication however has not been submitted in Switzerland up to now, therefore no risk minimization measures are applicable in Switzerland.

Table 5 describes the routine risk minimisation measures implemented for Rapiscan in EEA.

Table 5 Description of routine risk minimization activities for safety concern

Safety concern	Routine risk minimisation activities
Missing information Repeat use in FFR indication	- The EU SmPC was changed. Other risk minimisation measures beyond the product information: - prescription only medicine, - treatment with Rapiscan is restricted to use in a medical facility where cardiac monitoring and resuscitation equipment are available.

6.3. Additional risk minimisation measures

Routine risk minimisation activities as described in 3.2 are sufficient to manage the safety concerns of the medicinal product.

6.4. Summary table of risk minimisation measures

Table 6 presents a summary of the pharmacovigilance activities and risk minimisation activities with regard to use of Rapiscan in EEA. There are no safety concerns for Rapiscan in Switzerland which require risk minimisation measures.

Table 6 Summary table of pharmacovigilance activities and risk management activities for safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information Repeat use in FFR indication	Routine risk minimisation measures: - The EU SmPC was changed. - Rapiscan is prescription only medicine. Additional risk minimisation measures: - None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - targeted follow-up questionnaire. Additional pharmacovigilance activities: - none.

7. Planned studies in the Post-authorisation Pharmacovigilance Development

Table 7 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
Safety and Pharmacokinetic Study of Regadenoson in Paediatric Patients (GE262-001)	**Primary Objectives:** • To evaluate the safety and tolerability of a single, body-weight (weight category) adjusted intravenous (i.v.) bolus dose of regadenoson in paediatric patients aged 1 month to <18 years and who weigh at least 3 kg. • To characterise the pharmacokinetics (PK) of a single, body-weight (weight category) adjusted i.v. dose of regadenoson and the effects on heart rate (HR) in 3 paediatric populations: adolescents aged 12 to <18 years, children aged 2 to <12 years, and infants aged 1 to <24 months, and who weigh at least 3 kg.	The evaluation of safety and tolerability of a single, body-weight (weight category) adjusted intravenous (i.v.) bolus dose of regadenoson in paediatric patients aged 1 month to <18 years	Planning	Start date: December 2020 Recruitment end: 2025 Final report: 2026

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	Secondary Objectives: • To determine the relationship between regadenoson PK variables/exposure and changes in HR, including impact of patient factors. • To determine the associated myocardial hyperaemic response after administration of regadenoson using dynamic first-pass perfusion magnetic resonance imaging (MRI) and quantitative myocardial perfusion reserve (MPR) analysis.			

Summary of changes to the Risk Management Plan over time

Table 8 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
12.0	28 Nov 2019	To reflect that fatal myocardial infarction was included in the warning section of the SmPC, and data to support this change in SVII.3. To reflect that hypersensitivity, including anaphylaxis, was included in the warning section of the SmPC. To reflect the changed wording in the SmPC related to the warning to avoid methylxanthines in patients who experience seizure after regadenoson use. The safety profile has been updated and the following risks have been removed from the list of safety concerns: SA/AV nodal block, Myocardial Ischaemia, Cerebrovascular accident, Elevated Blood Pressure and hypertensive crisis, Hypotension, Worsening or recurrence of atrial fibrillation, Hypersensitivity, Prolongation of regadenoson induced seizures following aminophylline, Seizure, Respiratory compromise (bronchoconstriction and respiratory arrest), Off-label use involving exercise, Safety in patients with prolonged QT syndrome, Safety in pregnancy, Safety in lactation, and Safety in children.	The overall safety profile has not changed.
11.0	27 August 2019 (EMA/452535/2019)	Additional safety concern (missing information): Safety of repeated dose in FFR. The risk “Interaction with dipyridamole”, previously classified as important identified risk, was removed from the list of safety concerns based on the lack of reports of drug interaction with dipyridamole in the PSUR with DLP 09 April 2017.	The RMP was also updated to align with Guideline on Good Pharmacovigilance practices: Module V – Risk management systems (Rev 2).
10.0	May 2017	Updates to reflect the proposed indication of FFR and completion of PASS 401 study (01-1-401)	The overall safety profile has not changed.
9.0	June 2016	Updates to clinical and post-marketing exposures and completion of Study 3606-CL-3004 (redacted synopsis in Annex 9)	

Table 8 Summary of changes to the Risk Management Plan over time

8.0	May 2015	Updates to combine respiratory arrest and bronchoconstriction under a single important identified risk "Respiratory compromise (bronchoconstriction and respiratory arrest)"	RMP updated in line with the PRAC PSUR assessors report for PSUR#8 EMEA/H/C/PSUSA/00 002616/201410 dated 07 May 2015
7.0	October 2014	Updates regarding the additional risk minimization measure of a Direct Healthcare Professional Communication.	RMP updated in line with the PRAC Rapporteur preliminary assessment report EMEA/H/C/001176/PSUV/0015 dated 05 Sep 2014-Request for supplementary information
6.0	May 2014	Added "Cerebrovascular accident (CVA)" and "prolongation of regadenoson induced seizures following aminophylline" as important identified risks. Reclassified "elevated blood pressure" to "elevated blood pressure and hypertensive crisis".	RMP updated in line with the PRAC Rapporteur final report EMEA/H/C/001176/PS U 012 dated 08 May 2014
5.0	December 2013	Added "Seizures", "worsening/recurrence of atrial fibrillation" and "elevated blood pressure" as important identified risks and "CVA" as an important potential risk	RMP updated to reflect the current "Guidance on format of the risk management plan (RMP) in the EU – in integrated format" (25 July 2013, EMA/465932/2013 Rev.1).
4.0	June 2013	Added "hypersensitivity" as an important identified risk and included "off-label use involving exercise" as an important potential risk. Added 3606-CL-3004 to post-authorization development plan.	RMP updated to new RMP template according to 2012 EU PV legislation.
3.0	July 2011	Dyspnoea and headache were removed as identified risks. Results of the Phase 3b study evaluating the effect of caffeine intake on Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI) in subjects administered regadenoson (Study 3606-CL-3002) were included.	
2.0	At time of authorisation of Marketing Authorization Holder transfer to RPS EU Ltd 11/01/2011	Details of the PASS study were updated. Results of the Phase 4 studies investigating the safety and tolerance of regadenoson in subjects with asthma or chronic obstructive pulmonary disease (Study 3606-CL-3001) or renal impairment (Study 3606-CL-3010) were	MAH RPS EU Ltd adopts RMP of prior MAH Gilead Sciences and updates as appropriate.

Table 8 Summary of changes to the Risk Management Plan over time

		included. Safety in patients with renal impairment was removed from list of missing information.	
1.1	At time of Marketing Authorization 07/09/2010	**Identified Risks:** SA/AV nodal block Myocardial ischemia Hypotension Dyspnoea Headache Interaction with dipyridamole **Potential Risks:** Bronchoconstriction **Missing Information:** Safety in children Safety in pregnancy Safety in lactation Safety in patients with hepatic disease Safety in patients with renal impairment Safety in patients with prolonged QT syndrome	Gilead Sciences International Ltd (MAH) at time of Rapiscan Marketing Authorization.

References:

[Clinical Study Report Regadenoson 2016]
Clinical Study Report Regadenoson – 060912001. Comparison of Regadenoson (Rapiscan®) and Central Intravenous Adenosine for Measurement of Fractional Flow Reserve. Investigator Initiated Trial. Document on File.

[Townsend et al. 2017]
Townsend R, Desai A, Rammelsberg D, Kowalski D, Simmons N, Kitt TM. Safety and tolerability of intravenous regadenoson in healthy subjects: A randomized, repeat-dose, placebo-controlled study. J Nucl Cardiol 2017;24:57-65.

[van Nunen et al. 2015]
van Nunen LX, Lenders GD, Schampaert S, van 't Veer M, Wijnbergen I, Brueren GR, Tonino PA, Pijls NH. Single bolus intravenous regadenoson injection versus central venous infusion of adenosine for maximum coronary hyperaemia in fractional flow reserve measurement. EuroIntervention. 2015 Dec;11(8):905-13.