Rapiscan

Solution for Injection

GE Healthcare

Generic name: Regadenoson

RISK MANAGEMENT PLAN

Version: 12

Date of report: 20 November 2019

Marketing Authorisation Holder:

GE Healthcare AS
Nycoveien 1-2, P.O. Box 4220 Nydalen, NO-0401 Oslo, Norway

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE(s)	Adverse Event(s)
AdoR	Adenosine Receptor
AMR	Arlington Medical Resource
AV	Atrioventricular
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBF	Coronary Blood Flow
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CVA	Cerebrovascular accident
DBP	Diastolic Blood Pressure
ECG	Electrocardiography
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
FAME	Fractional Flow Reserve Versus Angiography for Multivessel Evaluation
FFR	Fractional flow reserve
HR	Heart Rate
IKr	Rapid component of the delayed rectifier potassium current
IKs	Slow component of the delayed rectifier potassium current
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MAH	Marketing Authorization Holder
MI	Myocardial Infarction
MPI	Myocardial Perfusion Imaging
MRI	Magnetic Resonance Imaging
MRHD	Maximum Recommended Human Dose
NICE	National Institute for Clinical Excellence
PASS	Post-Authorization Safety Study
PCI	Percutaneous Coronary Intervention
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PSUR	Periodic Update Safety Report
PTCA	Percutaneous Transluminal Coronary Angioplasty
RMP	Risk Management Plan
SA	Sinoatrial
SBP	Systolic Blood Pressure
SER	Signal Evaluation Report
SmPC	Summary of Product Characteristics
SMQ	Standard Medical Dictionary for Regulatory Activities Query
SPECT	Single-Photon Emission Computerized Tomography
UK	United Kingdom
US	United States

EU RISK MANAGEMENT PLAN FOR RAPISCAN (REGADENOSON)

RMP version to be assessed as part of this application:

RMP Version number:	Version 12
Data lock point for this RMP:	31 July 2019
Date of final sign off:	20 November 2019
Rationale for submitting an updated RMP:	The MAH committed to update the RMP, implementing revision 2 of GVP module V.
Summary of significant changes in this RMP:	Alignment with Guideline on Good Pharmacovigilance Practices: Module V – Risk management systems (Rev 2). Some risks previously classified as important identified and important potential risks were reclassified and removed from the list of safety concerns because no further characterization of the risks is required. The risks are followed up via routine PV activities and no additional risk minimisation measures or additional PV activities are required.
Other RMP versions under evaluation:	N/A

Details of the currently approved RMP:

Version number:	Version 11.0
Approved with procedure:	EMEA/H/C/001176/II/0034/G
Date of approval (opinion date):	27 August 2019
QPPV name:	Burkhard Roessink (MD)
QPPV signature	

PART I: PRODUCT OVERVIEW

Active substance(s) (INN or common name)	Regadenoson
Pharmacotherapeutic group(s) (ATC Code)	Cardiac therapy, other cardiac preparations, ATC code: C01EB21
Marketing Authorisation Holder	GE Healthcare AS
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Rapiscan
Marketing authorisation procedure	Centralised procedure
Brief description of the product	**Chemical class** – Regadenoson is a low-affinity (Ki ≈ 1.3 µM), selective agonist for the A_{2A} adenosine receptor (AdoR), with at least 10-fold lower affinity for the A_1-AdoR (Ki > 16.5 µM), and very low, if any, affinity for the A_{2B}-and A_3-AdoR.
	Summary of mode of action – Activation of the A2A adenosine receptor produces coronary vasodilation and increases coronary blood flow (CBF). The duration of effect of regadenoson to increase CBF is adequate for that needed for investigation of myocardial perfusion defects using radionuclide imaging in the clinic.
	Important information about its composition – Rapiscan is a clear colourless solution containing 5ml, 80 micrograms (µg) regadenoson/ml – total 400 µg regadenoson. – The excipients to be included are disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, propylene glycol disodium edetate, and water for injections
Hyperlink to the Product Information	Link to latest approved product information
Indication(s) in the EEA	**Current:** This medicinal product is for diagnostic use only. Rapiscan is a selective coronary vasodilator for use in adults as a pharmacological stress agent for: – radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress. – the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated (see sections 4.2 and 5.1).
	Proposed: N/A
Dosage in the EEA	**Current:** The recommended dose is a single injection of 400 micrograms regadenoson (5 ml) into a peripheral vein, with no dose adjustment necessary for body weight. *Repeated use* For use in radionuclide MPI: This product is to be administered only once within a 24-hour period. For use in FFR: This product is to be administered no more than twice, no less than 10 minutes apart, during any 24-hour period. When administered

	twice 10 minutes apart in a 24-hour period, full safety data for the second injection of Rapiscan are not available. No dose adjustment is necessary for patients that are elderly, and that have hepatic or renal impairment. The safety and efficacy of regadenoson in children below the age of 18 years have not yet been established.
	Proposed: N/A
Pharmaceutical form(s) and strengths	**Current:** Solution for injection. Each 5 ml vial contains 400 micrograms regadenoson (80 micrograms/ml).
	Proposed: N/A
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

Coronary Artery Disease

Rapiscan is a selective coronary vasodilator for use in adults as a pharmacological stress agent for:

- radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.
- the measurement of fractional flow reserve (FFR) of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated Incidence

Coronary atherosclerosis is a progressive disease, which begins in childhood in Western countries, but with overt clinical symptoms of myocardial ischemia resulting from Coronary artery disease (CAD) (e.g., angina, myocardial infarction [MI]) not evident until mid to late adulthood.

Accurate data on the prevalence of CAD across Europe are not readily available; however, an analysis of pooled longitudinal data collected from several European countries provides the incidence of coronary heart disease (CHD) events (coronary death, MI, and angina pectoris) over a 10-year period in males 40-59 years of age at the start of the study (study entry 1958-1964). Among the 2,213 males in northern Europe (Finland, Netherlands), the 10-year incidence was 177 events/1000, which was much greater than the incidence (67/1000) among 5,897 males from southern Europe (Italy, Croatia, Serbia, Greece) [Menotti et al. 2000]. In the ARIC study in participants aged from 45 to 64 years, the average age-adjusted CAD incidence rates per 1000 person-years were 12.5 in white men and 10.6 in black men [Jones et al. 2002].

The 10-year incidence rates of death due to CHD in northern European cohorts from a longitudinal study were much greater (51/1000) than in the southern Europe cohorts (19/1000) [Menotti et al. 2000].

The standardised death rates in 28 European Union (EU) countries for men in 2013 were higher than those for women. This was 176.2 and 98.8 per 100 000 male/female inhabitants respectively [Eurostat 2013].

Prevalence

The prevalence of atherosclerosis by age group was estimated in a Norwegian population (The Tromsø Study) [Joakimsen et al. 1999], using the prevalence of carotid atherosclerotic plaques as detected by ultrasound Table 1). Among 6,420 men and women 25-84 years of age, the percent of patients with plaques increased progressively with age, from 1.7-3.0% in the 25-34 age group to 76.5-81.2% in those 75-84 years of age. The prevalence was higher in males aged 25-74 years of age, but this gender trend was not evident in the elderly (75-84 years of age). The pattern of atherosclerotic plaques in this European population reflects the pattern

for the prevalence of CAD in the US population and is expected to reflect the prevalence of CAD across Europe.

Table 1 Percent of Norwegian Study Population with Plaques

Age Range (years of age)											
25-34		**35-44**		**45-54**		**55-64**		**65-74**		**75-84**	
Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
3.0	1.7	14.9	10.8	32.0	18.2	52.2	40.3	69.4	61.0	76.5	81.2

Source: The Tromsø Study: 1994-1995 [Joakimsen et al. 1999]

Demographics of the target population in the authorized indication – age, gender and risk factors for the disease

Data from France, Germany, Italy, Spain and the UK in 2007, show that radionucleotide stress testing is primarily a procedure for older patients, with peak usage in the 50-64-year-old age group. Only 0.2% of radionucleotide stress tests were performed in female patients aged 18-29, and 11.0% in females aged 30-49 [Arlington Medical Resources 2007].

The use of radionuclide MPI in adults generally increases with age, similar to the pattern for the prevalence of CAD (Table 2); however, use of radionuclide MPI peaks in the 50-64 year age group with fewer procedures in older patients (≥ 65 years of age), despite higher prevalence of CAD in the older population. More males than females under 50 years of age undergo radionuclide MPI; above 50 years of age, a similar or greater percent of females undergo MPI. The pattern of pharmacologic stress use with age parallels that for use of radionuclide MPI.

Table 2 Radionuclide and Pharmacologic Stress MPI Procedures in France, Germany, Italy, Spain and UK in 2007: Percentage Distribution by Age and Gender

Age Range (years)										
Type	**18-29**		**30-49**		**50-64**		**65-74**		**≥75**	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Radionuclide MPI (%)	0.4	0.2	14.5	11.0	42.3	40.6	32.1	32.8	10.7	15.4
	0.3		13.2		41.6		32.4		12.5	
Pharm Stress MPI (%)	0.2		8.6		36.6		34.5		20.1	

Source: Arlington Medical Resources Inc; The myocardial perfusion Study Market Guide, annualized based on Q2/Q4 2007 (France, Germany, Italy, Spain and United Kingdom) [Arlington Medical Resources 2007].

Risk factors for CAD include age, a family history of CAD, and lifestyle choices. Risk factors that may be influenced by lifestyle include hypertension, hypercholesteremia, type 2 diabetes, obesity, and smoking [NICE CG95 2010] National Institute for Clinical Excellence (NICE) Clinical guideline 95. March 2010, Chest pain of recent onset. London, UK. [Nichols et al. 2012].

Patients with recent onset chest pain commonly require a highly sensitive and specific diagnostic test to detect the presence / absence of CAD. In the United Kingdom, the NICE published a technology appraisal in 2003, [NICE TA73 2003], recommending MPI as an initial diagnostic tool in patients suspected in having CAD whom an exercise electrocardiography (ECG) test is likely to be unreliable or impossible, in diabetics, or at low-risk of having CAD.

Recently this guidance was partially updated by the NICE clinical guideline on chest pain of recent onset, whereby assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin, single-photon emission computerized tomography (SPECT) MPI is recommended as one of the diagnostic tools for people with suspected CAD with a pre-test probability of CAD of 30-60%.

Pressure derived FFR appears to be a useful index to monitor and guide coronary intervention, particularly adequate stent deployment [Pijls et al. 1998]. Its diagnostic accuracy to predict inducible ischaemia correctly was approximately 95% and exceeded the diagnostic accuracy of thallium exercise testing and dobutamine stress ECG when performed as single tests [Pijls et al. 1996]. The use of FFR to guide coronary intervention has been demonstrated to improve patient outcomes (death, MI, and urgent revascularization) and health resource utilization [Fearon et al. 2010].

The main existing treatment options

In Radionuclide Myocardial Perfusion Imaging

The currently marketed pharmacological stress agents for use in MPI, adenosine (Adenoscan®) and dipyridamole (Persantin) are administered as intravenous (IV) infusions and are associated with side effects due to activation of non-A2A-adenosine receptor (AdoR) subtypes. These include atrioventricular (AV) nodal block (A1-AdoR), hypotension (A2A- and A2B-AdoR), and the provocation respiratory compromise, bronchoconstriction and respiratory arrest, (A2B- and A3-AdoR). Regadenoson is a selective A2A-AdoR agonist that is less likely than adenosine or dipyridamole to activate non-A2A-AdoR subtypes and hence has less potential to cause serious outcomes related to the activation of these receptors. The incidence of side effects with the other pharmacological stress agents is considered appropriate for measuring the background incidence of the identified and potential risks that are or may be associated with regadenoson.

For the measurement of Fractional Flow Reserve

Although the use of FFR to guide coronary intervention has been demonstrated to improve patient outcomes (death, MI, and urgent revascularization) and health resource utilization [Fearon et al. 2010], there is no pharmacological stress agent approved for use to cause maximum hyperaemia during the measurement of FFR. There is evidence that demonstrates the utility of FFR using adenosine to cause maximum hyperaemia and inform the decision to perform revascularization or to manage symptoms with medical therapy. As regadenoson was discovered and developed to overcome the undesirable features of adenosine by selectively stimulating the A2A-AdoR with the rapid physiologic evaluation of susceptible coronary artery stenosis when using peripheral vein, injection of regadenoson offers a practical procedural advantage in patients undergoing radial access for percutaneous coronary intervention (PCI) where a central line catheter for adenosine administration is not available.

Natural history of the indicated condition in the population, including mortality and morbidity

Patients are referred to undergo a MPI study predominately by cardiologists (80%), but non-cardiac physicians (11%), primary care physicians (5%) and surgeons, cardiac and non-cardiac, (4%) also refer patients [Reyes et al. 2012]. The most common reason for referral were for the diagnosis of CAD (56%), followed by assessment of known disease (39%) and myocardial viability and hibernation (5%) [Reyes et al. 2012].

Patients who undergo a MPI study for the diagnosis of CAD and are unable to exercise adequately (defined as to 85% of their age-predicted maximum heart rate) are at a higher risk for subsequent death and MI than those able to exercise [Shaw et al. 2012]. Furthermore, the results of the diagnostic MPI study can be used to further stratify patients to those with high or low risk of subsequent death or MI; namely, patients with myocardial perfusion defects as detected by MPI are at greater risk of death and MI. For exercising patients with a preserved resting Left ventricular ejection fraction (LVEF) >45%, 2-year CAD death or MI event-free survival ranged from 99.4% to 89% for 0% to ≥20% ischemic myocardium. Those at highest risk included patients undergoing pharmacologic stress with depressed LVEF. For pharmacologic stress patients with a resting LVEF ≤45%, 2-year CAD death or MI event-free survival ranged from 89% to 48% for 0% to ≥20% ischemic myocardium [Shaw et al. 2012].

The benefit of measuring the functional consequence of a coronary artery stenosis to reduce death, MI, and urgent revascularization persists for up to 15 years after the index event and reduces overall costs and healthcare resource utilization associated with treatment of patients with known or suspected CAD [Fearon et al. 2010]. The FAME 2 (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2) study showed that the percentage of patients who had a primary endpoint event is significantly smaller in PCI group than in the medical-therapy group [De Bruyne et al. 2012].

Important co-morbidities

In the regadenoson phase 3 studies, the most common cardiovascular histories included hypertension (81%), prior revascularization procedure of coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA) or stenting (51%), angina (63%), history of MI (41%) or arrhythmia (33%); other medical history included diabetes (32%) and Chronic Obstructive Pulmonary Disease (COPD) (5%). Patients with a recent history of serious uncontrolled ventricular arrhythmia, MI, or unstable angina, a history of greater than 1st degree AV block, or with symptomatic bradycardia, sick sinus syndrome, or a heart transplant were excluded. Several patients took cardioactive medications on the day of the scan, including β-blockers (18%), calcium channel blockers (9%), and nitrates (6%). Based on the results of the initial adenosine MPI study, 68% of patients had 0-1 segments showing reversible defects (out of 17 left ventricular segments), 24% had 2-4 segments, and 9% had ≥ 5 segments. Approximately 54% of patients had renal impairment (CL_{CR} less than 80 mL/min; see also Part II SIV.3 - Limitations in respect to populations typically under-represented in clinical trial development programmes).

Severe hepatic impairment

From experience with regadenoson Phase 3 studies, it is estimated that approximately 2% of patients receiving regadenoson may have underlying hepatic impairment defined as a prothrombin time above 1.5 times the ULN (in patients who were not taking warfarin) and/or a total plasma bilirubin level above 1.5 times ULN, or an elevation of aspartate aminotransferase or alanine aminotransferase greater than 2.5 times ULN.

For patients with severe liver impairment who are awaiting liver transplant, there is evidence from published literature that the proportion of these patients with at least one critical coronary artery stenosis is up to 26%, and at least half of these patients will die perioperatively of cardiac complications [Mandell et al. 2008]. Identifying such patients is therefore important, and screening for CAD using pharmacological stress MPI may become more common [Bradley et al. 2010].

Module SII - Non-clinical part of the safety specification

The development program for regadenoson includes a comprehensive series of non-clinical pharmacology, pharmacokinetic, and toxicology studies that support the safety of the product for the intended single-dose IV use. In particular, the results of the acute-dose studies and the 7- and 28-day repeat-dose studies in rats and dogs, the in vivo and in vitro mutagenicity

studies, the teratology studies in rats and rabbits, and the special studies to evaluate the potential for irritation at the site of injection of the drug product and the toxicity of drug substance impurities, indicate that there are no adverse systemic effects that would preclude the intended IV clinical use of regadenoson. Table 3 presents the significant safety findings for regadenoson from non-clinical studies and relevance to human usage.

Table 3 Significant safety findings for regadenoson from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Toxicity	
Reproductive toxicity Reproductive studies were conducted in rabbits and rats using multiple consecutive doses of regadenoson that were 2 to 20 times (rats) and 4 to 20 times (rabbits) the maximum recommended human dose (MRHD), based on body surface area comparison. Foetal developmental delays were reported in both species at doses of 0.5 mg/kg/day (20 x MRHD for rabbits and 10 x MRHD for rats). Signs of maternal toxicity were observed in rats at doses of 0.5 mg/kg/day (10 x MRHD) and in rabbits at doses of 0.1 mg/kg/day (4 x MRHD). Regadenoson administered at doses up to 0.8 mg/kg/day to pregnant rats (16 x MRHD) and up to 0.5 mg/kg/day to pregnant rabbits (20 x MRHD) during organogenesis was not teratogenic. There have been no studies of regadenoson related to transplacental transfer or excretion in milk.	The maternal toxicity is a possible explanation for the observed foetal developmental delays. Because animals received daily repeat doses of regadenoson during the gestational period, their exposure was significantly higher than that achieved with the standard single dose administered to humans for use in radionuclide MPI. The likelihood of regadenoson being used in pregnant or breast-feeding mothers is expected to be unlikely or very low; the Summary of Product Characteristics (SmPC) states that regadenoson should not be given during pregnancy unless clearly necessary. Data from France, Germany, Italy, Spain and the UK in 2007, show that radionucleotide stress testing is primarily a procedure for older patients, with peak usage in the 50-64-year-old age group. Only 0.2% of radionucleotide stress tests were performed in female patients aged 18-29, and 11.0% in females aged 30-49.
Developmental toxicity /Fetotoxicity Foetal developmental delays were reported in rabbits and rats at doses of 0.5 mg/kg/day (20 x MRHD) for rabbits and 10 x MRHD for rats). These doses were maternally toxic. The developmental No Effect Level in rats was 0.1 mg/kg/day (2 x MRHD). The developmental No Effect Level in rabbits was 0.3mg/Kg/day (12 x MRHD).	The doses at which foetal development delays were identified were 10-20 times higher than the maximum recommended doses for humans and were repeated during the pregnancy. Therefore, the overall exposure in animals was much higher and of longer duration than would be expected in clinical use. The doses were also maternally toxic. The maternal toxicity is a possible explanation for the observed foetal developmental delays. Therefore, the relevance of these data to human use is limited.

Table 3 Significant safety findings for regadenoson from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Safety pharmacology	
Cardiovascular Regadenoson is a low-affinity (Ki ≈ 1.3 μM), selective A2A-AdoR agonist, with at least 10-fold lower affinity for the A1-AdoR (Ki > 16.5 μM), and very low, if any, affinity for the A2B- and A3-AdoR (see MAA Section 2.6.2). Activation of the A2A- AdoR by regadenoson produces coronary vasodilation and increases CBF. Despite low affinity for the A2A-AdoR, regadenoson has high potency for increasing coronary vasodilation in rat and guinea pig isolated hearts. Regadenoson causes a large, reversible, and dose-dependent coronary vasodilation in rodents, pigs, and dogs. Regadenoson shows greater selectivity (≥215- fold) than adenosine for increasing coronary conductance (A2A-mediated response) relative to slowing of cardiac AV nodal conduction (A1- mediated response) in the guinea pig heart. Regadenoson causes dilation of systemic arterial vascular beds and hence, can decrease mean arterial blood pressure, but its vasodilatory potency in limb, pulmonary, and brain vascular beds in the dog is less than its coronary vasodilator effect.	These effects are consistent with the results of receptor binding assays indicating that regadenoson is a selective A2A-AdoR agonist. The duration of CBF increase following IV bolus administration of regadenoson is short and consistent with that needed for the detection of myocardial perfusion defects using radionuclide imaging in the clinic. Regadenoson was developed as a short-acting pharmacologic stress agent (administered as a single 0.4 mg IV bolus) in conjunction with radionuclide MPI because it has low yet selective affinity for the A2A-AdoR, has high potency for increasing CBF, and preferentially causes greater coronary than peripheral vasodilatation in animal models. Thus, regadenoson has the potential to selectively increase CBF, while minimizing some of the side effects caused by the currently approved pharmacologic stress agents, via the selective activation of the receptor responsible for the coronary vasodilatory effect of adenosine (i.e., the A2A-AdoR) and not the other AdoR subtypes (e.g., the A1-AdoR in the heart and the A2B-AdoR on mast cells).

Table 3 Significant safety findings for regadenoson from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Regadenoson transiently increases HR in rats and in dogs. QT: Regadenoson was found to have no effect on the rapid component of the delayed rectifier potassium current (IKr) as determined by measuring the effect of regadenoson (5 µM) on the human ether-a-go-go related gene (hERG) tail current in HEK 293 cells stably transfected with hERG cDNA or on action potential parameters, including duration and triangulation, upstroke amplitude, and resting membrane potential in dog isolated Purkinje fibres paced at rates of 0.5 and 1 Hz (regadenoson, 0.05–10 µM). These results were confirmed by results of two secondary pharmacodynamic studies on the effects of regadenoson on dog left ventricular (LV) myocytes and female rabbit isolated hearts. Regadenoson (up to 10 µM) did not significantly affect the rapid component of the delayed rectifier potassium current (IKr) or the slow component of the delayed rectifier potassium current (IKs) in dog isolated LV myocytes and regadenoson (up to 30 µM) did not alter LV monophasic action potential duration in female rabbit isolated hearts. These findings indicate that regadenoson is unlikely to alter the functions of ion channels in the ventricular myocardium. Furthermore, regadenoson (5 to 10 mg/kg) caused no significant changes of QT interval in the heart in which HR was kept constant via physiological or pharmacological procedures, indicating that regadenoson has no direct effect on the QT interval.	Regadenoson dose dependently increases HR in humans, although the magnitude of HR increase is known to be variable [Hage et al. 2011]. The effect of regadenoson to increase HR is believed to be, at least in part, a sympathoexcitatory effect mediated by activation of the A2A-AdoR on afferent nerve endings in the carotid and aortic bodies, i.e., chemoreceptor activation [Costa et al. 1993], [Dibner-Dunlap et al. 1993] . Regadenoson related increase in heart rate by sympathetic stimulation causes a shortening of the QT interval. In a patient with a long QT syndrome, sympathetic stimulation can result in less shortening of the QT interval than is normal and may even cause a paradoxical increase in the QT interval. In these patients, the phenomenon of R-on-T syndrome can occur; wherein an extra beat interrupts the T wave of the previous beat, and this increases the risk of a ventricular tachyarrhythmia. Exercise is also known to increase sympathetic tone to increase heart rate, BP and cause an increase in CBF proportional to the increase in cardiac demand. The effect of pharmacological stress in combination with exercise may be additive.
Nervous system: Regadenoson doses of 2 and 40 µg/kg, IV caused no change in motor activity or body temperature. Consistent with the effect of regadenoson to decrease MAP, higher doses of regadenoson (80, 200, and 400 µg/kg, IV) caused a reduction in body temperature (-2.1%, - 4.9%, and -7.2 %, respectively) compared to the control group. Also observed were transient reductions in motor activity after doses of 200 and 400 µg/kg (recovery noted by 2 h post dose) and a decrease in abdominal tone after the highest 400 µg/kg dose (recovery noted by 3 h post dose).	There have been no adverse events that have been reported during the clinical development of regadenoson. However unresponsive to stimuli and catatonia have been reported in post- marketing surveillance. The post marketing cases were associated with labelled events of syncope, symptomatic hypotension, symptomatic bradycardia, seizure or TIA.

Table 3 Significant safety findings for regadenoson from non-clinical studies

Key Safety findings (from non- clinical studies)	Relevance to human usage
Pulmonary: Regadenoson had no biologically relevant effect on pulmonary function at the 80 and 200 µg/kg IV doses	Regadenoson is a selective A_{2A} adenosine receptor agonist. The A_{2B} and A_3 adenosine receptors have been implicated in the pathophysiology of respiratory compromise, bronchoconstriction and respiratory arrest. In in vitro studies, regadenoson has been shown to have little binding affinity for the A2B and A3 adenosine receptors. The incidence of a FEV1 reduction > 15% from baseline after Rapiscan administration was assessed in three randomised, controlled clinical studies where it was shown to occur no more frequently versus placebo. Dyspnoea did not correlate with a decrease in FEV1.
Mechanisms for drug interactions Regadenoson is not known to inhibit the metabolism of substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 in human liver microsomes, Regadenoson itself is not a substrate for these enzymes. Following intravenous administration of ^{14}C-radiolabelled regadenoson to rats and dogs, most radioactivity (85-96%) was excreted (predominately by the kidney) in the form of unchanged regadenoson.	Regadenoson is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 enzymes nor are the pharmacokinetics of regadenoson likely to be altered by substrates or inhibitors of these cytochrome P450 enzymes. These findings indicate that metabolism of regadenoson does not play a major role in the elimination of regadenoson. In healthy volunteers, 57% of the regadenoson dose is excreted unchanged in the urine (range 19-77%), with an average plasma renal clearance around 450 ml/min, i.e., in excess of the glomerular filtration rate. This indicates that renal tubular secretion plays a role in regadenoson elimination.
Other toxicity-related information or data	Not applicable

Additional non-clinical studies are not planned for the medicinal product.

Summary of the findings from non-clinical testing

Safety concerns:

Important identified risks (confirmed by clinical data):

None identified.

Important potential risks (not refuted by clinical data or which are of unknown significance):

Foetal developmental delays were observed in rats and rabbits which were exposed up to 20 times the MRHD. Signs of maternal toxicity were also observed in both the species. The maternal toxicity is a possible explanation for the observed foetal developmental

delays. Because animals received daily repeat doses of regadenoson during the gestational period, their exposure was significantly higher than that achieved with the standard single dose administered to humans.

Missing information:

There is no information regarding hepatic impairment, pregnancy, lactation, fetotoxicity, exercise and the use of regadenoson in the non-clinical data.

Module SIII - Clinical trial exposure

Regadenoson used as a pharmacological stress agent for radionuclide myocardial perfusion imaging in adult patients unable to undergo adequate exercise stress

Overall cumulative subject exposure is provided in Table 4, inclusive of Pre-Approval Clinical Studies Phase 1 through 3 and Completed Post-Approval Clinical Studies by Study Phase - Phase 3 through 4. Table 5 presents clinical trial exposure by dose, Table 6 by age group and gender, and Table 7 by ethnic or racial origin, based upon exposure data from completed studies.

Most subjects (2,807) received one dose of regadenoson and 1,489 subjects received two doses of regadenoson. The proposed marketed dose of 400 µg was administered to a total of 4,531 subjects in completed clinical trials as of 09 Apr 2014.

Table 4 Duration of exposure

Duration of exposure (at least)	Persons	Person-days
1 dose	2,807	2,807
2 doses	1,489	2,970*
3 doses	17	17*
Total	**4,313**	**5,802**

Studies included CVT 5111, CVT 5112, CVT 5121, CVT 5122, CVT 5123, CVT 5124, CVT 5125, CVT 5126, CVT 5131, CVT 5132, 3606-CL-3001, 3606-CL-3010, 3606-CL-3002, CVT 5127, 3606-CL-2001 and 3606-CL-1005, 3606-CL- 3004

* In 3606-CL-1005 8 and 17 subjects received 2 and 3 doses of regadenoson 10 minutes apart, respectively.

Table 5 By dose

Dose of exposure in 24 hrs	Persons	Person-days
< 0.4 mg	51	71*
0.4 mg	4,531	5,986*
0.5 mg	24	24
> 0.5 mg	32	48*
Total	**4,313**	**5,802**

Studies included CVT 5111, CVT 5112, CVT 5121, CVT 5122, CVT 5123, CVT 5124, CVT 5125, CVT 5126, CVT 5131, CVT 5132, 3606-CL-3001, 3606-CL-3010, 3606-CL-3002, CVT 5127, 3606-CL-2001 and 3606-CL-1005, 3606-CL- 3004

* In 3606-CL-1005 8 subjects received 2 doses (0.4mg each) of regadenoson 10 minutes apart, 8 subjects received 3 doses (0.1mg each) of regadenoson 10 mins apart, and 9 subjects received 3 doses (0.2mg each) of regadenoson 10 minutes apart

Exposure by age and gender is presented in Table 6. Due to different methods of data collection within the studies conducted prior to first approval and those conducted after first approval, race or ethnicity (Table 7, Table 8 and Table 9) are organised by Pre- and post-approval studies. Person-day exposure by age and race or ethnicity were not summarised within the final study reports.

Table 6 By age group and gender

Age group	Persons		Person days	
	M	F	M	F
<18 years*	0	0	0	0
18 to 44 years*	179	120	230	133
45 to 64 years*	811	511	908	546
18-64**	409	302	788	578
65 to 74 years	789	422	1,062	559
75 years and older	476	270	621	351
Total	**2,664**	**1,625**	**3,609**	**2,167**

Studies included CVT 5111, CVT 5112, CVT 5121, CVT 5122, CVT 5123, CVT 5124, CVT 5125, CVT 5126, CVT 5131, CVT 5132, 3606-CL-1005, 3606-CL-2001, 3606-CL-3001, 3606-CL-3002, 3606-CL-3004, and 3606-CL-3010.

* CVT 5111, CVT 5112, CVT 5121, CVT 5122, CVT 5123, CVT 5124, CVT 5125, CVT 5126, CVT 5131, CVT 5132, 3606-CL-2001, 3606-CL-3001, 3606-CL-3002, and 3606-CL-3010

** 3606-CL-1005 and 3606-CL-3004 only.

Table 7 By ethnic or racial origin

Ethnic/racial origin	Persons	Person days
Asian	95	99
Black/African American	96	96
Caucasian	1,295	1,357
Hispanic/Latino	128	129
Other	37	37
Total	**1,651**	**1,718**

Studies included CVT 5111, CVT 5112, CVT 5121, CVT 5122, CVT 5123, CVT 5124, CVT 5125, CVT 5126, CVT 5131, CVT 5132.

Table 8 By racial origin

Racial origin	Persons	Person days*
Asian	121	349
Black/African American	354	509
Caucasian	2,156	3,313
Other	29	43
Total	**2,660**	**4,214**

Studies included 3606-CL-2001, 3606-CL-3001, 3606-CL-3002, 3606-CL-3004, 3606-CL-3010, CVT-5127 and 3606-CL-1005.

Table 9 By ethnicity

Ethnic origin	Persons	Person days*
Non-Hispanic/Latino	2,256	3,404
Hispanic/Latino	403	674
Total	**2,659**	**4,078**

Studies included 3606-CL-2001, 3606-CL-3001, 3606-CL-3002, 3606-CL-3004, 3606-CL-3010, CVT-5127 and 3606-CL-1005

Exposure data in special populations from pivotal Phase 3 and Phase 4 studies have not been amalgamated and are shown separately. The Phase 3 CVT 5131 and CVT 5132 studies enrolled patients, typically known or suspected of having CAD, referred for stress imaging but, by design, patients with greater cardiac disease severity were over represented. The study population included a high percentage of patients with significant cardiovascular and other diseases/conditions including hypertension (> 80%), angina (~55%), unstable angina or MI, arrhythmias, diabetes and/or congestive heart failure (CHF) or had undergone CABG, PTCA, or stenting Table 10. The Phase 4 studies enrolled patients with asthma, COPD, or renal disease who represented likely candidates for MPI and also had a diagnosis of CAD or risk factors for CAD (e.g. hypertension, hypercholesterolemia, diabetes). Due to the difference in patient groups and method of collection demographic data, exposure by special population in the pivotal Phase 3 trials is presented in a separate table (Table 10) from the Phase 4 studies (Table 11).

Table 10 Special populations: Pivotal Phase 3 CVT 5131 and CVT 5132 studies

	Persons	Person time
Cardiovascular History		
CABG, PTCA, or Coronary Artery Stenting	675	675
MI	540	540
Arrhythmias	451	451
Diabetes	428	428

Table 10 Special populations: Pivotal Phase 3 CVT 5131 and CVT 5132 studies

	Persons	Person time
Unstable Angina	253	253
Intermittent Claudication or Stroke	250	250
Congestive Heart Failure	237	237
Chronic Obstructive Pulmonary Disease (COPD)	69	69
Left Ventricular Ejection Fraction		
35-50%	309/1,259	309
<35%	107/1,259	107
Renal impairment		
$CL_{cr} \geq 50$ and < 80 mL/min	490	490
$CL_{cr} \geq 30$ and < 50 mL/min	179	179
CL_{cr} < 30 mL/min	45	43
Hepatic impairment		
2.5x transaminase elevation or 1.5x elevation of serum bilirubin or prothrombin time	27/1,158	27
Total	**1,337**	**1,337**

Source: MAA CTD Module 5

Table 11 Special populations: Phase 4 studies

	Persons	Person time
Chronic kidney disease[1]	334	334
Stage III	287	287
Stage IV	47	47
Asthma[2]	386	386
Step 1	108	108
Step 2	33	33
Step 3	50	50
Step 4	86	86
Step 5	44	44
Step 6	0	0
Unable to assign	35	35
Chronic obstructive pulmonary disease (COPD)[3]	327	327

Table 11 Special populations: Phase 4 studies

	Persons	Person time
Stage I	44	44
Stage II	150	150
Stage III	60	60
Stage IV	4	4
Unable to assign	56	56
Cardiovascular history		
Coronary artery disease	235	235
Hypertension	809	809
Hypercholesterolemia	738	738
Metabolic syndrome		
Type 2 diabetes	363	363
Obesity	666	666
Smoking (≥ 10 pack-years)	529	529
Total	**1,006**	**1,006**

Source 3606-CL-3001 and 3606-CL-3010

[1] National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) Clinical Practice Guidelines for GFR.

[2] Baseline severity of asthma was classified using a modified version of the National Heart, Lung and Blood Institute Expert Panel Report 3 ([NHLBI Stepwise Approach for Managing Asthma in Youths ≥ 12 Years of Age and Adults.

[3] Global initiative for chronic obstructive lung disease (GOLD) criteria

No pregnant or lactating women or immuno-compromised patients were enrolled in any study. The presence of a genetic polymorphism of the A2A-AdoR was not determined in any study.

Regadenoson used for the measurement of FFR of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated

A total of 249 patients undergoing cardiac catheterization for the measurement of FFR received regadenoson (400 µg) intravenously from 2 independent clinical studies. Overall cumulative subject exposure by duration of exposure is provided in Table 12. Table 13 presents clinical trial exposure by dose.

Table 12 Duration of exposure

Duration of exposure (at least)	Persons	Person-days
1 dose	149	149
1 dose	12	12
2 doses*	88	88

Independent clinical studies included: [Stolker et al. 2015] and [van Nunen et al. 2015]
*In van [van Nunen et al. 2015] ([Clinical Study Report Regadenoson 2016]), 2 doses were administered 10 minutes apart

Table 13 By dose

Dose of exposure in 24 hrs	Persons	Person-days
400 µg	161	161
800 µg*	88	88

Independent clinical studies included: [Stolker et al. 2015] and [van Nunen et al. 2015]
*In [van Nunen et al. 2015] ([Clinical Study Report Regadenoson 2016]), 2 doses (400 µg each) were administered 10 minutes apart

Exposure by age and gender is presented in Table 14. Due to different methods of data collection within the studies conducted prior to first approval and those conducted after first approval, race or ethnicity (Table 15) are organised by Pre- and Post-approval studies. Person-day exposure by age and race or ethnicity were not summarised within the final study reports.

Table 14 By age group and gender

Age group	Persons		Person days	
	M	F	M	F
50 to 74 years	188	61	188	61

Independent clinical studies included: [Stolker et al. 2015] and [van Nunen et al. 2015]

Table 15 By ethnic or racial origin

Ethnic/racial origin	Persons	Person days
African-American	39	39
Caucasian	103	103
Other	6	6
Total	**148**	**148**

Independent clinical study included: [Stolker et al. 2015]

Exposure data in special populations from independent clinical studies have been amalgamated. These studies included patient with cardiovascular medical history of hypertension, previous MI and a history of CHF.

Table 16 Special populations: Independent clinical studies included Stolker 2015 and van Nunen 2015

Medical history (%)	[Stolker et al. 2015]	[van Nunen et al. 2015]
Hypertension	88	54
Previous MI	40	36
History of congestive heart failure	22	Not reported
Chronic Obstructive Pulmonary Disease (COPD)	14	Not reported
Dislipidemia/hypercholeremia	77	36
Diabetes mellitus	43	21
Active smoking	39	20
Prior PCI	58	43
Prior CABG	4	Not reported

Module SIV - Populations not studied in clinical trials

The target population studied in the Phase 3 program (CVT 5131 and CVT 5132) included patients who were clinically-indicated for a pharmacologic stress radionuclide SPECT MPI without exercise. All patients initially underwent a pharmacologic stress SPECT MPI study with adenosine before being randomized to undergo a second pharmacologic stress SPECT study with either adenosine or regadenoson. The Phase 3 protocol exclusion criteria (CVT 5131 and CVT 5132 final study reports) were designed to ensure that patients could safely receive adenosine and ensure that patients would have a stable clinical condition in the interval between the initial adenosine imaging study and the randomized study.

SIV.1 - Exclusion criteria in pivotal clinical studies within the development programme

Bronchoconstrictive and bronchospastic lung disease

Reason for exclusion: AdoR agonists may cause bronchoconstriction and respiratory compromise in patients with known or suspected bronchoconstrictive disease, COPD or asthma, for which adenosine is contraindicated.

Is it considered to be included as missing information? No

Rationale: Respiratory compromise (bronchoconstriction and respiratory arrest) is considered an important identified risk for regadenoson.

History of greater than first degree AV block or sick sinus syndrome without a functioning artificial pacemaker

Reason for exclusion: Contraindication to adenosine.

Is it considered to be included as missing information? No

Rationale: SA/AV nodal block is considered an important identified risk for regadenoson.

Severe hypotension

Reason for exclusion: Patients who are acutely ill with severe hypotension are not recommended to undergo a vasodilator stress MPI study.

Is it considered to be included as missing information? No

Rationale: Hypotension is considered an important identified risk for regadenoson.

Unstable angina that has not been stabilised with medical therapy

Reason for exclusion: Patients who are acutely ill with unstable angina not yet stabilized with medical therapy are not recommended to undergo a MPI study.

Is it considered to be included as missing information? No.

Rationale: Myocardial ischemia is considered an important identified risk for regadenoson.

Decompensated states of congestive heart failure

Reason for exclusion: Patients with decompensated state of CHF are not recommended to undergo a MPI study.

Is it considered to be included as missing information? No

Rationale: Respiratory compromise (bronchoconstriction and respiratory arrest) is considered an important identified risk for regadenoson.

Hypersensitivity to adenosine or its excipients

Reason for exclusion: Patients with known hypersensitivity to regadenoson or any of the excipients of Rapiscan should not receive Rapiscan.

Is it considered to be included as missing information? No

Rationale: Hypersensitivity is considered an important identified risk for regadenoson.

Patients 18 years of age or younger

Reason for exclusion: Practical and logistical reasons. A deferral of studies in all paediatric age groups was granted on 24 April 2009 (EMEA-000410-PIP01-08).

Is it considered to be included as missing information? Yes. A Paediatric Investigation Plan (PIP) study is being planned.

Rationale: Not applicable.

Females who are pregnant, breast feeding, or (if pre-menopausal), not practicing acceptable method of birth control

Reason for exclusion: Practical reasons.

Is it considered to be included as missing information? Yes

Rationale: Not applicable.

Consumption of any products containing methylxanthines or theophylline

Reason for exclusion: Methylxanthines (e.g., caffeine and theophylline) are non-specific AdoR antagonists and may interfere with the vasodilation activity of adenosine and regadenoson. Aminophylline (100 mg, administered by slow IV injection over 60 seconds) injected 1 minute after 400 micrograms regadenoson in subjects undergoing cardiac catheterisation, was shown to shorten the duration of the CBF response to regadenoson as measured by pulsed-wave Doppler ultrasonography (CVT 5121). Furthermore, aminophylline has been used to attenuate adverse reactions to regadenoson and adenosine (CVT 5131 and CVT 5132). Therefore, patients in the Phase 3 trials avoided consumption of any products containing methylxanthines (e.g. caffeine) as well as any medicinal products containing theophylline for at least 12 hours before administration of adenosine or regadenoson.

Is it considered to be included as missing information? No

Rationale: Not applicable.

SIV.2 - Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. Table 17 discusses limitations of ADR detection in the regadenoson clinical trial programme.

Table 17 Limitations of ADR detection

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare	A total of 3,142 subjects were exposed over the whole clinical trial programme.	The probability of detecting at least 1 subject with a rare ADR if there were no background incidence in the sample of 3,142 subjects is approximately 95% if the true rate is 1 in 1000 (80% probability if the true rate was 1 in 2,000)

Table 17 Limitations of ADR detection

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Due to prolonged exposure Due to cumulative effects Which have a long latency	This is not applicable as because in radionuclide MPI regadenoson is administered as a single unit dose drug over 10 seconds, only once within a 24-hour period. For FFR, regadenoson is administered no more than twice, no less than10 minutes apart, during any 24-hour period. Regadenoson has a terminal half-life of approximately 2 hrs.	ADRs due to prolonged exposure, drug accumulation, or long latency is not expected.

SIV.3 - Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 18 presents exposure in the populations of patients that were excluded or under-represented when the safety of regadenoson was studied in the clinical development programme.

Table 18 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children	Not included in the clinical development program. The EMA has adopted a decision (P/82/2009) granting a Paediatric Investigation Plan (PIP) for regadenoson in the diagnosis of myocardial perfusion disturbances and a deferral of studies in all paediatric age groups (24 April 2009; EMEA-000410-PIP01-08).
Pregnant women	Not included in the clinical development program The likelihood of regadenoson being used during pregnancy is expected to be unlikely or very low.
Breastfeeding women	Not included in the clinical development program. The likelihood of regadenoson being used in women who are breast-feeding is expected to be unlikely or very low.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	• Risk in patients with hepatic impairment was investigated in clinical studies CVT 5131 and CVT 5132 enrolling 28 subjects with impaired liver function. A post-authorization safety study (PASS) to assess the safety profile of regadenoson in patients with liver impairment was also conducted, the safety concern was subsequently removed.
• Patients with renal impairment	• CLcr ≥ 50 and < 80 mL/min - 490 subjects CLcr ≥ 30 and < 50 mL/min - 179 subjects CLcr < 30 mL/min - 45 subjects
• Patients with cardiovascular impairment: – Prolonged QT Syndrome	• Nine patients were treated with regadenoson in the Phase 3 program who had a baseline QTcF interval >500 msec.
• Immunocompromised patients	• Not included in the clinical development program
• Patients with a disease severity different from inclusion criteria in clinical trials – COPD and Asthma	• CVT 5125 - 49 patients with moderate to severe COPD, CVT 5124 - 48 patients with mild to moderate asthma who had previously been shown to have bronchoconstrictive reactions to adenosine monophosphate, 3606-CL-3001 - 1009 patients with mild or moderate asthma (n=537) and moderate or severe COPD (n=472).
Population with relevant different ethnic origin	Not included in the clinical development program. Regadenoson itself is not a substrate for the cytochrome P450 enzymes. Therefore, inter-ethnic differences in pharmacokinetics of drugs due to types and/or frequencies of gene variants coding for drug metabolising enzymes are of no consequence. The safety population examined during the pre-authorization studies consisted primarily of Caucasian patients (78%), with 8% Hispanics, 6% Asians, and 6% Blacks. This broadly reflects the anticipated marketed use of regadenoson.

Subpopulations carrying relevant genetic polymorphisms: • Single nucleotide polymorphisms (SNPs) of the adenosine A2A receptor (A2A-AdoR)	Not included in the clinical development program. There are two published reports studying the effect A2A AdoR gene SNP 1976 C>T polymorphism on the vasodilatory effect of adenosine [Riksen et al. 2007], [Andreassi et al. 2011].
Population requiring a repeated dose for the FFR indication	– 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. – 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], which was well balanced between treatment groups.

Module SV - Post-authorisation experience

SV.1 - Post-authorisation exposure

SV.1.1 - Method used to calculate exposure

Exposure to marketed drug has been calculated using data from available company report sales volume, in addition to data from the Arlington Medical Resource (AMR) Myocardial Perfusion Study, used to obtain data on usage by gender and the different age groups. For both methods, calculations are based on the assumption that one vial/syringe represents the average dosage for one patient regardless of body weight. The average dosage is based upon the 5 mL (0.08 mg/mL) recommended dose of regadenoson by rapid IV injection. Data presented below includes exposure through 09 April 2018.

It should be noted that the use of sales data for patient-day exposure calculations will tend to overestimate exposure, due to the accumulation of drug stocks at pharmacies/distributors. However, this method of estimating exposure to marketed product is felt to be justified because most patients receiving regadenoson will be adults receiving a single unit of regadenoson.

SV.1.2 - Exposure

As of 09 April 2018, a cumulative total of [redacted] units of Rapiscan (EEA and non-EEA excluding US) and [redacted] units of Lexiscan (US) were in commercial distribution in the Ex-US and US markets, respectively. The estimated cumulative worldwide exposure to regadenoson is 28,059,164 patients-days since US product launch on 09 June 2008 (Table 19). The extrapolated age and gender values (not actual prescriptions) based on obtained prescribing data applied to the US cumulative estimated patient exposure by patient-days is presented in Table 20.

Table 19 Geographical distribution of estimated patient exposure

Geographic Area	Patient-days
EU/EEA	606,844
Non-EU/EEA (excluding US)	[redacted]
US	
Total	**28,059,164**

Table 20 Estimated cumulative exposure by age and gender – United States*

	Sex			**Age**				**Dose**	**Formulation**
Indication	Male	Female	Total	0-17*	18-64	>65	Total	5 mL** (0.08 mg/mL)	IV
Coronary Artery Disease	[redacted]								
Total									

*US Marketing Experience only - Data Source: Internal Sales, The Myocardial Perfusion Study Market Guide – AMR

**Rapiscan and Lexiscan are commercially provided in a vial and pre-filled syringe respectively, of 0.4 mg in 5 mL for single use. Each patient indicated for Rapiscan or Lexiscan MPI receives only one entire vial or pre-filled syringe regardless of their body weight. Therefore, patient exposure may be estimated by a number of sold units.

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

It is unlikely that the product could be misused for an illegal purpose such as a recreational drug or for facilitating assault etc., as Rapiscan (regadenoson) is only available subject to a medical prescription.

Module SVII - Identified and potential risks

SVII.1 - Identification of safety concerns in the initial RMP submission

The safety concerns in the initial approved RMP, are presented in Table 21.

Table 21 List of safety concerns identified in the approved initial Rapiscan RMP*

Summary of safety concerns	
Important identified risks	SA/AV Nodal Block
	Myocardial Ischemia
	Hypotension
	Dyspnea
	Headache
	Interaction with dipyridamole
Important potential risks	Bronchoconstriction
Important missing information	Safety in Children
	Safety in Pregnancy
	Safety in lactation
	Safety in patients with renal impairment
	Safety in patients with severe hepatic impairment
	Safety in patients with bronchoconstrictive disease
	Safety in patients with prolonged QT syndrome

* EPAR- Public Assessment report for Rapiscan- Procedure No EMEA/H/C/001176

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for

which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

(i) Interactions with caffeine and theophylline

Methylxanthines are non-specific AdoR antagonists and may attenuate the MBF increase caused by the vasodilation activity of regadenoson. Caffeine has the potential to interfere with the activity of regadenoson and the identification of myocardial ischemia using radionuclide MPI, resulting in false-negative stress images. Because methylxanthines may interfere with the activity of regadenoson, it is recommended for patients to avoid consumption of products containing methylxanthines, including caffeinated coffee, tea or other caffeinated beverages, chocolate, and caffeine- and theophylline-containing drug products, for at least 12 hours before a scheduled radionuclide MPI.

(ii) Interactions with cardioactive drugs (beta-blockers, calcium channel blockers, ACE-inhibitors, nitrates, cardiac glycosides, angiotensin receptor blockers)

The cardioactive medications slow the heart rate (HR) and may decrease the ability of detecting relative hypoperfusion in diseased myocardium areas subjected to pharmacologic stress. The implications of medication effects ultimately depend on the reason for stress imaging. When stress testing is performed to detect the presence and extent of CAD, then it is advisable to discontinue anti- ischemic therapy before the test, especially if the test results will guide anti-ischemic therapy or interventions. Consideration should also be given to withdrawing medications when the purpose of the test is for risk stratification of known CAD, with limited prognostic data [Baghdasarian et al. 2007]. In contrast, when stress imaging is performed to evaluate the effectiveness of anti-ischemic therapy in stable CAD or low- risk patients with angina, it is reasonable to continue therapy, particularly in patients after procedures such as PCI or CABG.

SVII.1.2. Risks considered important for inclusion in the safety specification

There have been major changes to the Risk management plan over time and these changes have been described in Annex 8 – Summary of changes to the risk management plan over time.

SVII.2 - New safety concerns and reclassification with a submission of an updated RMP

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, and all safety concerns except one have been removed.

The safety concerns described below in Table 22 require no further characterization and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting. Further, additional risk minimisation measures were not and will not be

required. Therefore, they have been reclassified and are no longer included in the list of safety concerns.

Table 22 Summary of safety concerns to be 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

Further reasons and justifications for reclassification are provided below.

SA/AV nodal block, Myocardial ischemia, Elevated Blood Pressure and hypertensive crisis, Hypotension, Worsening or recurrence of atrial fibrillation

Regadenoson is contraindicated in some cardiac conditions such as: second or third degree atrioventricular (AV) block or sinus node dysfunction, unless these patients have a functioning artificial pacemaker; unstable angina that has not been stabilised with medical therapy; severe hypotension or decompensated states of heart failure, as per SmPC.

The cardiac safety profile of regadenoson is well established in Myocardial Perfusion Imaging (MPI) and it is not expected that the patient population is not very different from those indicated for the FFR testing. Its use is authorised under continuous ECG monitoring and should only be administered in a medical facility.

For these reasons, it is considered that these safety concerns are properly documented in the SmPC. There are no additional pharmacovigilance activities ongoing or planned; therefore, these safety concerns can be removed.

Hypersensitivity

Hypersensitivity reactions including rash, urticaria, angioedema and anaphylaxis are listed in the SmPC of regadenoson. It is also included as a contraindication the hypersensitivity to the active substance or to any of the excipients in section 4.3. Additional pharmacovigilance activities are not required, at this moment.

Seizures

This safety concern is well documented in the product information of regadenoson, as well as a warning to use with caution when regadenoson is administered to patients with a history of seizures or other risk factors for seizures, including concomitant medications. No additional pharmacovigilance activities are considered necessary at this time.

Prolongation of regadenoson-induced seizures following administration of aminophylline

It is known that aminophylline should not be used solely for the purpose of terminating a seizure induced by regadenoson, as per SmPC. In fact, a DHPC was developed and disseminated after the 2nd Updated PSUR PRAC Assessors Report. No additional pharmacovigilance actions are ongoing or planned.

Respiratory compromise (bronchoconstriction and respiratory arrest):

This important identified risk is properly documented in the product information of regadenoson, including also information related to support measures in case a respiratory compromise will be developed.

Off-label use involving exercise

It is known that the use of regadenoson in combination to exercise can lead to hypotension, hypertension, syncope and cardiac arrest. This information is included in the SmPC and there are no ongoing or planned additional pharmacovigilance activities.

Safety in children

Regadenoson is not indicated in children, as per SmPC. Coronary artery disease is a disease most likely to be frequent in older population, therefore, regadenoson is not expected to be used in children.

Safety in pregnancy

Fetotoxicity, but not teratogenicity, was noted in embryo-fetal development studies. Regadenoson is a product for diagnostic use only not expected to be used during pregnancy. Consequently, there are no ongoing or planned pharmacovigilance activities to study the safety profile of regadenoson in this specific population either additional risk minimization measures.

Safety in lactation

In breast-feeding women, it is not expected either the exposure to regadenoson. In any case, according to SmPC, it is recommended not breast-feed for at least 10 hours following regadenoson administration. No additional pharmacovigilance activities are deemed necessary at the moment.

Safety in patients with prolonged QT syndrome

No enough patients with this medical condition were included in clinical trials of regadenoson. Because a regadenoson radionuclide MPI test may be indicated for patients who also have long QT syndrome, the proposed SmPC includes a warning about the risk of ventricular tachyarrhythmias in patients with a long QT syndrome. Additional pharmacovigilance activities have not been required, at this moment.

SVII.3 - Details of important identified risks, important potential risks, and missing information

SVII.3.1. - Presentation of important identified risks and important potential risks

No important identified or potential risks are identified for regadenoson.

SVII.3.2. - Presentation of the missing information

Safety of repeated use in FFR indication

Evidence source:
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.

Anticipated risk/consequence of the missing information: is expected to be low.

Module SVIII - Summary of the safety concerns

Table 23 below presents a summary of the safety concerns identified for Rapiscan.

Table 23 Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Safety of repeated use in FFR indication

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concern "safety of repeated use in FFR measurement"

The routine pharmacovigilance activities for Rapiscan include request for additional information about safety of repeated use in FFR measurement by using a targeted follow-up questionnaire (Annex 4 - Specific adverse drug reaction follow-up forms). The objective is to ensure that all reports concerning safety concern are carefully assessed so that additional measures can be introduced if justified by emerging data.

Other forms of routine pharmacovigilance activities

None proposed.

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

This section is not applicable to Rapiscan as no post-authorisation efficacy studies are planned or ongoing.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 - Routine Risk Minimisation Measures

Table 24 describe the routine risk minimisation measures implemented for safety concern for Rapiscan.

Table 24 Description of routine risk minimization activities for safety concern

Safety concern	Routine risk minimisation activities
Missing information Repeat use in FFR indication	Routine risk communication: - SmPC sections 4.2, 5.1, and 5.2, - PL section 3. 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.

V.2 - Additional risk minimisation measures

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

V.3 - Summary table of risk minimisation measures

Table 25 presents a summary of the pharmacovigilance activities and risk minimisation activities with regard to use of Rapiscan.

Table 25 Summary table of pharmacovigilance activities and risk management activities for safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Repeat use in FFR indication	Routine risk minimisation measures: - SmPC sections 4.2, 5.1 and 5.2, - 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 - 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. Additional risk minimisation measures: - None proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - targeted follow-up questionnaire. Additional pharmacovigilance activities: - none.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of the risk management plan for Rapiscan (regadenoson)

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

Rapiscan SmPC and its package leaflet give essential information to healthcare professionals and patients on how Rapiscan should be used.

This summary of the RMP for Rapiscan 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 Rapiscan RMP.

I. The medicine and what it is used for

Rapiscan is authorized as a selective coronary vasodilator for use in adults as a pharmacological stress agent for radionuclide MPI in patients unable to undergo adequate exercise stress. It is also used for the measurement of FFR of a single coronary artery stenosis during invasive coronary angiography, when repeated FFR measurements are not anticipated (see SmPC for the full indication). It contains regadenoson as the active substance and it is given by IV route of administration.

Further information about the evaluation of Rapiscan benefits can be found in Rapiscan 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/rapiscan.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimise the risks identified for medicinal products:

- 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 packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The legal status of medicine - 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 Rapiscan is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Rapiscan are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Rapiscan. 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	None
Missing information	Safety of repeated use in FFR indication

II.B Summary of important risks

Missing information: Safety of repeated use in FFR indication	
Risk minimisation measures	<u>Routine risk minimisation measures:</u> - SmPC sections 4.2, 5.1 and 5.2, - 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 - 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. <u>Additional risk minimisation measures:</u> - None proposed.

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 Rapiscan.

II.C.1 Other studies in post-authorisation development plan

There are no studies required for Rapiscan.

PART VII: ANNEXES

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Annex 4 - Specific adverse drug reaction follow-up forms

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)Annex 7 - Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Annex 4 - Specific adverse drug reaction follow-up forms

Repeat use in FFR: targeted follow-up questionnaire

Patient Initials First/Middle/Last	Date of Birth Day/Month/Year	Gender Male/female	Age Years	Weight Kg	Height cm	Race/Ethnicity

1. Please provide the following information for repeat use of regadenoson in FFR study

Indication for repeat dose (e.g., due to duration of hyperemia, anatomical reasons, FFR, other)	
Time from first dose of regadenoson to repeat dose	
Description of the event(s)	
Interval between adverse event(s) and repeat dose	
Duration of event	
Was treatment provided for the event(s), if yes, please describe	
Outcome of the event(s): (resolved, resolving, ongoing)	

2. Please provide, from the following classification(s), the status of coronary artery disease (CAD) before use of regadenoson

Classification	Maximal Stenosis	Interpretation	Patient
CAD-RADS 0	0%	No CAD	☐ No ☐ Yes
CAD-RADS 1	1 – 24%	Minimal non-obstructive	☐ No ☐ Yes
CAD-RADS 2	25 – 49%	Mild non-obstructive	☐ No ☐ Yes

CAD-RADS 3	50 – 69%	Moderate stenosis	☐ No ☐ Yes
CAD-RADS 4	A: 70 – 99% or B: Left Main >50% or 3-vessel ≥ 70%	Severe stenosis	☐ No ☐ Yes
CAD-RADS 5	100%	Total coronary occlusion	☐ No ☐ Yes
CAD-RADS N	Non-diagnostic	Obstructive CAD cannot be excluded	☐ No ☐ Yes
Please specific the involved coronary vessel(s): (LAD, RCA etc.)			

3. Please check the applicable boxes for patient's medical history (if not included in the AE report).

Does patient have a history of the following	☐ No ☐ Yes ☐ Unknown Congestive heart failure (CHF) ☐ No ☐ Yes ☐ Unknown Myocardial infarction (MI) ☐ No ☐ Yes ☐ Unknown Diabetes Mellitus ☐ No ☐ Yes ☐ Unknown Hypertension ☐ No ☐ Yes ☐ Unknown Hyperlipidemia ☐ No ☐ Yes ☐ Unknown Obesity ☐ No ☐ Yes ☐ Unknown Smoking ☐ No ☐ Yes ☐ Unknown Congenital heart disease ☐ No ☐ Yes ☐ Unknown Pulmonary disease/impairment ☐ No ☐ Yes ☐ Unknown Renal disease/impairment ☐ No ☐ Yes ☐ Unknown Liver disease ☐ No ☐ Yes ☐ Unknown Dehydration Other relevant medical conditions: _____

	_____ _____

4. Please provide patient's concomitant medications (if not included in the AE report)

In case of unknown indication for repeat use, and if used for FFR, a routine follow-up questionnaire will be sent. Three follow-up attempts will be performed before the case will be closed.

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

Not applicable.