ANNEX 1

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rapiscan 400 microgram solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml vial contains 400 micrograms regadenoson (80 micrograms/ml).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

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

- 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).

4.2 Posology and method of administration

Treatment with Rapiscan is restricted to use in a medical facility where cardiac monitoring and resuscitation equipment are available.

Posology
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.

Patients should avoid consumption of any products containing methylxanthines (e.g. caffeine) as well as any medicinal products containing theophylline for at least 12 hours before Rapiscan administration (see section 4.5).

When possible, dipyridamole should be withheld for at least two days prior to Rapiscan administration (see section 4.5).

Aminophylline may be used to attenuate severe and/or persistent adverse reactions to regadenoson but should not be used solely for the purpose of terminating a seizure induced by Rapiscan (see section 4.4).

Regadenoson causes a rapid increase in heart rate (see sections 4.4 and 5.1). Patients should remain sitting or lying down and be monitored at frequent intervals after the injection until the ECG parameters, heart rate and blood pressure have returned to pre-dose levels.

Repeated use
For use in MPI: This product is to be administered only once within a 24-hour period. Safety and tolerability of repeated use of this product within 24 hours has not been characterised.

For use in FFR: This product is to be administered no more than twice, no less than10 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.

Paediatric population

The safety and efficacy of regadenoson in children below the age of 18 years have not yet been established.

No data are available.

Elderly
No dose adjustment is necessary (see section 5.2).

Hepatic impairment
No dose adjustment is necessary (see section 5.2).

Renal impairment
No dose adjustment is necessary (see section 5.2).

Method of administration

For intravenous use.
Myocardial perfusion imaging (MPI):

- Rapiscan should be administered as a rapid, 10-second injection into a peripheral vein using a 22-gauge or larger catheter or needle.
- 5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection should be administered immediately after the injection of Rapiscan.
- The MPI acquisition protocol should be in line with clinical practice guidelines.

Fractional flow reserve (FFR):

- Rapiscan should be administered as a rapid 10-second injection into a peripheral vein, using a 22-gauge or larger catheter or needle
- 10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection should be administered immediately after the injection of Rapiscan.
- FFR should be measured as the lowest value of Pd/Pa achieved during steady state hyperemia.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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.
- Decompensated states of heart failure.

4.4 Special warnings and precautions for use

Regadenoson has the potential to cause serious and life-threatening reactions, including those listed

below (see also section 4.8). Continuous ECG monitoring should be performed and vital signs should be monitored at frequent intervals until the ECG parameters, heart rate and blood pressure have returned to pre-dose levels. Regadenoson should be used with caution and should only be administered in a medical facility with cardiac monitoring and resuscitation equipment. Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow intravenous injection (50 mg to 100 mg over 30-60 seconds) to attenuate severe and/or persistent adverse reactions to regadenoson but should not be used solely for the purpose of terminating a seizure induced by regadenoson.

Myocardial ischaemia
Fatal cardiac arrest, life-threatening ventricular arrhythmias, and myocardial infarction may result from the ischaemia induced by pharmacologic stress agents like regadenoson.

Regadenoson should be used with caution in patients with recent myocardial infarction.
Single Photon Emission Computed Tomography (SPECT) MPI clinical trials conducted with regadenoson excluded patients with recent (within 3 months) myocardial infarction.
Clinical trials for the measurement of FFR excluded patients with an acute myocardial infarction, or within 5 days of an acute myocardial infarction.

Sinoatrial and atrioventricular nodal block
Adenosine receptor agonists including regadenoson can depress the sinoatrial (SA) and AV nodes and may cause first, second or third degree AV block, or sinus bradycardia.

Hypotension
Adenosine receptor agonists including regadenoson induce arterial vasodilation and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency.

Elevated blood pressure
Regadenoson may cause clinically significant increases in blood pressure, which in some patients can lead to hypertensive crisis (see section 4.8). The risk of significant increases in blood pressure may be higher in patients with uncontrolled hypertension. Consideration should be given to delaying regadenoson administration until blood pressure is well controlled

Combination with exercise
Use of regadenoson involving exercise has been associated with serious adverse reactions including hypotension, hypertension, syncope and cardiac arrest. Patients who have had any symptoms or signs suggestive of acute myocardial ischaemia during exercise or recovery are likely to be at especially high risk of serious adverse reactions.

Transient ischaemic attacks and cerebrovascular accident
Regadenoson can cause transient ischaemic attack (see section 4.8). In post-marketing experience there have also been reports of cerebrovascular accident (CVA).

Risk of seizure
Caution should be used when administering regadenoson to patients with a history of seizures or other risk factors for seizures, including the concomitant administration of medicinal products that lower seizure threshold (e.g. antipsychotics, antidepressants, theophyllines, tramadol, systemic steroids and quinolones).

Aminophylline should be used with caution in patients with a history of seizures or who have other risk factors for seizures as it may prolong a seizure or cause multiple seizures because of its proconvulsant effect. Therefore administration of aminophylline solely for the purpose of terminating a seizure induced by regadenoson is not recommended.

Atrial fibrillation or flutter
Regadenoson should be used with caution in patients with a history of atrial fibrillation or flutter. In

post- marketing experience there have been cases of worsening or recurrence of atrial fibrillation after administration of regadenoson.

Bronchoconstriction
Regadenoson may cause bronchoconstriction and respiratory arrest (see section 4.8) , especially in patients with known or suspected bronchoconstrictive disease, chronic obstructive pulmonary disease (COPD) or asthma. Appropriate bronchodilator therapy and resuscitative measures should be available prior to regadenoson administration.

Long QT syndrome
Regadenoson stimulates sympathetic output and may increase the risk of ventricular tachyarrhythmias in patients with a long QT syndrome.

Warnings related to excipients
This medicinal product contains less than1 mmol sodium (23 mg) per dose. However, the injection of sodium chloride 9 mg/ml (0.9%) solution given after regadenoson contains 45 mg of sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Methylxanthines
Methylxanthines (e.g., caffeine and theophylline) are non-specific adenosine receptor antagonists and may interfere with the vasodilation activity of regadenoson (see section 5.1). Patients should avoid consumption of any medicinal products containing methylxanthines as well as any medicinal products containing theophylline for at least 12 hours before regadenoson administration (see section 4.2).

Dipyridamole
Dipyridamole increases blood adenosine levels and the response to regadenoson may be altered when blood adenosine levels are increased. When possible, dipyridamole should be withheld for at least two days prior to regadenoson administration (see section 4.2).

Cardioactive medicinal products
In clinical studies, regadenoson was administered to patients taking other cardioactive medicinal products (i.e., β-blockers, calcium channel blockers, ACE inhibitors, nitrates, cardiac glycosides, and angiotensin receptor blockers) without apparent effects on the safety or efficacy profile of regadenoson.

Other interactions
Regadenoson does not inhibit the metabolism of substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 in human liver microsomes, indicating that it is unlikely to alter the pharmacokinetics of medicinal products metabolised by these cytochrome P450 enzymes.

Regadenoson does not significantly inhibit the transporters OAT1, OAT3, OCT1, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, BSEP, ENT 1 or ENT2 at 1 µM. The data are insufficient to conclude about the risk of interactions at the level of these transporters given that a single concentration was evaluated in most instances.

Regadenoson may have a modest inhibitory effect on the active renal transporter, OCT2, and has been found to be likely substrate for BCRP, ENT1 or ENT2 mediated transport. However, given the proposed duration of use, the effects of the drug transporters are unlikely to be clinically relevant.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of regadenoson in pregnant women. Animal studies on pre- and post-natal development have not been conducted. Fetotoxicity, but not teratogenicity, was noted in embryo-fetal development studies (see section 5.3). The potential risk for humans is unknown. Regadenoson should not be used during pregnancy unless clearly necessary.

Breast-feeding
It is unknown whether regadenoson is excreted in human breast milk. The excretion of regadenoson in milk has not been studied in animals. A decision should be made whether to discontinue breast-feeding or to abstain from regadenoson administration taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. If regadenoson is administered, the woman should not breast-feed for at least 10 hours (that is, at least 5 times the plasma elimination half-life) following regadenoson administration.

Fertility
Fertility studies with regadenoson have not been performed (see section 5.3).

4.7 Effects on ability to drive and use machines

Regadenoson administration may result in adverse reactions such as dizziness, headache, and dyspnoea (see section 4.8) soon after administration. However, most adverse reactions are mild and transient, resolving within 30 minutes after receiving regadenoson. Therefore, regadenoson would be expected to have no or negligible influence on the ability to drive or use machines once treatment has been completed and these reactions have resolved.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions in most patients receiving regadenoson in clinical trials were mild, transient (usually resolving within 30 minutes after receiving regadenoson) and required no medical intervention. Adverse reactions occurred in approximately 80% of patients. The most common adverse reactions reported during clinical development in a total of 1,651 patients/subjects were: dyspnoea (29%), headache (27%), flushing (23%), chest pain (19%), electrocardiogram ST segment changes (18%), gastrointestinal discomfort (15%) and dizziness (11%).

Regadenoson may cause myocardial ischaemia (potentially associated with fatal cardiac arrest, life-threatening ventricular arrhythmias, and myocardial infarction), hypotension leading to syncope and transient ischaemic attacks, elevated blood pressure leading to hypertension and hypertensive crises, and SA/AV node block leading to first, second or third degree AV block, or sinus bradycardia requiring intervention (see section 4.4). Signs of hypersensitivity (rash, urticaria, angioedema, anaphylaxis and/or throat tightness) may be immediate or delayed onset. Aminophylline may be used to attenuate severe or persistent adverse reactions to regadenoson but should not be used solely for the purpose of terminating a seizure induced by regadenoson (see section 4.4).

Tabulated list of adverse reactions
Assessment of adverse reactions for regadenoson is based on safety data from clinical studies and post-marketing experience. All adverse reactions are presented in the table below and are listed by system organ class and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Immune system disorders:	
Uncommon	Hypersensitivity reactions including: Rash, urticaria, angioedema, anaphylaxis and/or throat tightness.
Psychiatric disorders:	
Uncommon	Anxiety, insomnia
Nervous system disorders:	
Very common	Headache, dizziness
Common	Paraesthesia, hypoaesthesia, dysgeusia

Uncommon	Convulsions, syncope, transient ischaemic attack, unresponsiveness to stimuli, depressed level of consciousness, tremor, somnolence
Rare	Cerebrovascular accident
Eye disorders:	
Uncommon	Vision blurred, eye pain
Ear and labyrinth disorders:	
Uncommon	Tinnitus
Cardiac disorders:	
Very common	Electrocardiogram ST segment changes
Common	Angina pectoris, atrioventricular block, tachycardia, palpitations, other ECG abnormalities including electrocardiogram QT corrected interval prolonged
Uncommon	Cardiac arrest, myocardial infarction, complete AV block, bradycardia, atrial flutter, new-onset, worsening or recurrence of atrial fibrillation
Vascular disorders:	
Very common	Flushing
Common	Hypotension
Uncommon	Hypertension, pallor, peripheral coldness
Respiratory, thoracic and mediastinal disorders:	
Very common	Dyspnoea
Common	Throat tightness, throat irritation, cough
Uncommon	Tachypnoea, wheezing
Not known	Bronchospasm, Respiratory arrest
Gastrointestinal disorders:	
Very common	Gastrointestinal discomfort
Common	Vomiting, nausea, oral discomfort
Uncommon	Abdominal distension, diarrhoea, faecal incontinence
Skin and subcutaneous tissue disorders:	
Common	Hyperhidrosis
Uncommon	Erythema
Musculoskeletal and connective tissue disorders:	
Common	Back, neck or jaw pain, pain in extremity, musculoskeletal discomfort
Uncommon	Arthralgia
General disorders and administration site conditions:	
Very common	Chest pain
Common	Malaise, asthenia
Uncommon	Pain at injection site, general body pain

Description of selected adverse reactions

Fatal cardiac arrest, life-threatening ventricular arrhythmias and myocardial infarction may result from the ischaemia induced by pharmacologic stress agents. Cardiac resuscitation equipment and trained staff should be available before administering regadenoson (see section 4.4).

Sinoatrial and atrioventricular nodal block

Regadenoson, can depress the SA and AV nodes and may cause first, second or third degree AV block, or sinus bradycardia requiring intervention. In clinical trials first degree AV block (PR prolongation > 220 msec) developed in 3% of patients within 2 hours of regadenoson administration; transient second degree AV block with one dropped beat was observed in one patient receiving regadenoson. In postmarketing experience, third degree heart block and asystole have been reported within minutes of regadenoson administration.

Hypotension

Adenosine receptor agonists, including regadenoson induce arterial vasodilation and hypotension. In clinical trials, decreased systolic blood pressure (> 35 mm Hg) was observed in 7% of patients and decreased diastolic blood pressure (> 25 mm Hg) was observed in 4% of patients within 45 minutes of regadenoson administration. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease,

pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency. In postmarketing experience, syncope and transient ischaemic attacks have been reported.

Elevated blood pressure
In clinical trials, increased systolic blood pressure (≥ 50 mm Hg) was observed in 0.7% of patients and increased diastolic blood pressure (≥ 30 mm Hg) in 0.5% of patients. Most increases resolved within 10 to 15 minutes, but in some cases, increases were observed at 45 minutes following administration.

Long QT syndrome
Regadenoson increases sympathetic tone, which causes an increase in heart rate and 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.

Headache
Headache was reported by 27% of subjects who received regadenoson in clinical trials. The headache was considered severe in 3% of subjects.

Elderly population
Older patients (≥ 75 years of age; n = 321) had a similar adverse reaction profile compared to younger patients (< 65 years of age; n = 1,016), but had a higher incidence of hypotension (2% *versus* < 1%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were assessed as intolerable at regadenoson doses greater than 0.02 mg/kg.

Treatment

Aminophylline may be used to attenuate severe or persistent adverse reactions to regadenoson. Administration of aminophylline, solely for the purpose of terminating a regadenoson-induced seizure is not recommended (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations, ATC code: C01EB21

Mechanism of action

Regadenoson is a low affinity agonist ($K_i \approx 1.3$ µM) for the A_{2A} adenosine receptor, with at least 10-fold lower affinity for the A_1 adenosine receptor ($K_i > 16.5$ µM), and very low, if any, affinity for the A_{2B} and A_3 adenosine receptors. Activation of the A_{2A} adenosine receptor produces coronary vasodilation and increases coronary blood flow (CBF). Despite low affinity for the A_{2A} adenosine receptor, regadenoson has high potency for increasing coronary conductance in rat and guinea pig isolated hearts, with EC_{50} values of 6.4 nM and 6.7-18.6 nM, respectively. Regadenoson shows selectivity (≥ 215-fold) for increasing coronary conductance (A_{2A}-mediated response) relative to

slowing of cardiac AV nodal conduction (A_1-mediated response) as measured by AV conduction time (rat heart) or the S-H interval (guinea pig heart). Regadenoson preferentially increases blood flow in coronary relative to peripheral (forelimb, brain, pulmonary) arterial vascular beds in the anaesthetised dog.

Pharmacodynamic effects

Coronary blood flow
Regadenoson causes a rapid increase in CBF which is sustained for a short duration. In patients undergoing coronary catheterisation, pulsed-wave Doppler ultrasonography was used to measure the average peak velocity (APV) of CBF before and up to 30 minutes after administration of regadenoson (400 micrograms, intravenously). Mean APV increased to greater than twice baseline by 30 seconds and decreased to less than half of the maximal effect within 10 minutes (see section 5.2).

Myocardial uptake of the radiopharmaceutical is proportional to CBF. Because regadenoson increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, regadenoson causes relatively less uptake of the radiopharmaceutical in vascular territories supplied by stenotic arteries. Myocardial radiopharmaceutical uptake after regadenoson administration is therefore greater in areas perfused by normal relative to stenosed arteries. The same applies to the FFR measurement where the maximal myocardial blood flow is decreased in presence of severe coronary artery stenosis.

Myocardial perfusion imaging (MPI)
Haemodynamic effects
The majority of patients experience a rapid increase in heart rate. The greatest mean change from baseline (21 bpm) occurs approximately 1 minute after administration of regadenoson. However, heart rate increases of up to 42 bpm are reported in the literature (discussed below in the CMR MPI section). Heart rate returns to baseline within 10 minutes. Systolic blood pressure and diastolic blood pressure changes were variable, with the greatest mean change in systolic pressure of −3 mm Hg and in diastolic pressure of −4 mm Hg approximately 1 minute after regadenoson administration. An increase in blood pressure has been observed in some patients (maximum systolic blood pressure of 240 mm Hg and maximum diastolic blood pressure of 138 mm Hg).

Respiratory effects
The A_{2B} and A_3 adenosine receptors have been implicated in the pathophysiology of bronchoconstriction in susceptible individuals (i.e., asthmatics). In *in vitro* studies, regadenoson has been shown to have little binding affinity for the A_{2B} and A_3 adenosine receptors. The incidence of a FEV_1 reduction > 15% from baseline after regadenoson administration was assessed in three randomised, controlled clinical studies. In the first study in 49 patients with moderate to severe COPD, the rate of FEV_1 reduction > 15% from baseline was 12% and 6% following regadenoson and placebo dosing, respectively (p=0.31). In the second study in 48 patients with mild to moderate asthma who had previously been shown to have bronchoconstrictive reactions to adenosine monophosphate, the rate of FEV_1 reduction > 15% from baseline was the same (4%) following both regadenoson and placebo dosing. In the third study in 1009 patients with mild or moderate asthma (n=537) and moderate or severe COPD (n=472) the incidence of FEV_1 reduction >15% from baseline was 1.1% and 2.9% in patients with asthma (p=0.15) and 4.2% and 5.4% in patients with COPD (p=0.58) following regadenoson and placebo dosing, respectively. In the first and second studies, dyspnoea was reported as an adverse reaction following regadenoson dosing (61% for patients with COPD; 34% for patients with asthma) while no subjects experienced dyspnoea following placebo dosing. In the third study dyspnoea was reported more frequently following regadenoson (18% for patients with COPD; 11% for patients with asthma) than placebo, but at a lower rate than reported during clinical development (see Section 4.8). A relationship between increased severity of disease and the increased incidence of dyspnoea was apparent in patients with asthma, but not in patients with COPD. The use of bronchodilator therapy for symptoms was not different between regadenoson and placebo. Dyspnoea did not correlate with a decrease in FEV_1.

Fractional Flow Reserve (FFR)

Haemodynamic Effects

In the measurement of FFR, the time to peak maximum hyperaemia was 30±13 seconds. The mean duration of hyperaemic plateau was 163 (±169) seconds and maximum hyperaemia lasted at least 19 seconds in 90% of patients, however, in the individual patient the duration of hyperaemia varied between 10 seconds to more than 10 minutes. Hyperaemia may fluctuate between sub-maximum and maximum until it slowly vanishes. The 10-second window of steady state hyperaemia can be too short for performing extensive pressure pullback recordings to assess complex or diffuse coronary artery disease. Repeat dosing within 10 minutes – except in patients where the duration of hyperaemia lasted for more than 10 minutes – caused a similar effect on peak and duration of maximum hyperaemia.

Clinical efficacy and safety

Clinical studies have demonstrated the efficacy and safety of regadenoson in patients indicated for pharmacologic stress Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), Cardiac Magnetic Resonance (CMR) and MultiDetector Computed Tomography (MDCT) MPI and for the measurement of FFR.

Regadenoson-stress SPECT MPI

The efficacy and safety of regadenoson for regadenoson-stress SPECT MPI were determined relative to adenosine in two randomised, double-blind studies (ADVANCE MPI 1 and ADVANCE MPI 2) in 2,015 patients with known or suspected coronary artery disease who were referred for a clinically-indicated pharmacologic stress MPI. A total of 1,871 of these patients had images considered valid for the primary efficacy evaluation, including 1,294 (69%) men and 577 (31%) women with a median age of 66 years (range 26-93 years of age). Each patient received an initial stress scan using adenosine (6-minute infusion using a dose of 0.14 mg/kg/min, without exercise) with a gated SPECT (single photon emission computed tomography) imaging protocol. After the initial scan, patients were randomised to either regadenoson or adenosine, and received a second stress scan with the same SPECT protocol as that used for the initial scan. The median time between scans was 7 days (range of 1-104 days).

The most common cardiovascular histories included hypertension (81%), coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA) or stenting (51%), angina (63%), and history of myocardial infarction (41%) or arrhythmia (33%); other medical history included diabetes (32%) and COPD (5%). Patients with a recent history of serious uncontrolled ventricular arrhythmia, myocardial infarction, or unstable angina, a history of greater than first degree AV block, or with symptomatic bradycardia, sick sinus syndrome, or a heart transplant were excluded. A number of patients took cardioactive medicinal products on the day of the scan, including β-blockers (18%), calcium channel blockers (9%), and nitrates (6%).

Comparison of the images obtained with regadenoson to those obtained with adenosine was performed as follows. Using the 17-segment model, the number of segments showing a reversible perfusion defect was calculated for the initial adenosine study and for the randomised study obtained using regadenoson or adenosine. In the pooled study population, 68% of patients had 0-1 segments showing reversible defects on the initial scan, 24% had 2-4 segments, and 9% had ≥ 5 segments. The agreement rate for the image obtained with regadenoson or adenosine relative to the initial adenosine image was calculated by determining how frequently the patients assigned to each initial adenosine category (0-1, 2-4, 5-17 reversible segments) were placed in the same category with the randomised scan. The agreement rates for regadenoson and adenosine were calculated as the average of the agreement rates across the three categories determined by the initial scan. The ADVANCE MPI 1 and ADVANCE MPI 2 studies, individually and combined, demonstrated that regadenoson is similar to adenosine in assessing the extent of reversible perfusion abnormalities:

	ADVANCE MPI 1 (n = 1,113)	**ADVANCE MPI 2 (n = 758)**	**Combined Studies (n = 1,871)**
Adenosine – Adenosine Agreement Rate (± SE) Number of Patients (n)	61 ± 3% 372	64 ± 4% 259	62 ± 3% 631
Adenosine – regadenoson Agreement Rate (± SE) Number of Patients (n)	62 ± 2% 741	63 ± 3% 499	63 ± 2% 1,240
Rate Difference (regadenoson – Adenosine) (± 95% Confidence Interval	1 ± 4% -7.5, 9.2%	-1 ± 5% -11.2, 8.7%	0 ± 3% -6.2, 6.8%

In ADVANCE MPI 1 and ADVANCE MPI 2, the Cicchetti-Allison and Fleiss-Cohen weighted kappas of the median score of three blinded readers with respect to ischaemia size category (not counting segments with normal rest uptake and mild/equivocal reduction in stress uptake as ischaemic) for the combined studies of regadenoson with the adenosine scan were moderate, 0.53 and 0.61, respectively; as were the weighted kappas of two consecutive adenosine scans, 0.50 and 0.55, respectively.

Regadenoson-stress PET MPI

Intraindividual comparison of regadenoson (0.4 mg/ 5 ml bolus) versus dipyridamole (0.57 mg/kg for 4 minutes) was performed in a prospective study recruiting 32 subjects (23 males and 9 females, mean age of 62 ± 12.1). From those, 26 had a reversible perfusion defect already identified on a previous clinically indicated dipyridamole-stress PET study with 82RbCl and 6 subjects with <5% pre-test likelihood for CAD showed no defects on dipyridamole PET images. The study included patients with a mild-moderate degree of ischemia with a small proportion of patients having moderate to severe ischemia, and they had normal or near-normal left ventricular function.
In this study the 82RbCl infusion started promptly after regadenoson injection (that is, imaging started 2 minutes following start of 82Rb infusion). Visual interpretation of PET images indicated no difference in the number of segments with reversible defects between regadenoson and dipyridamole for 30/32 image pairs.
Results may not be generalizable to patients with slowed circulation times associated with left or right heart failure, pulmonary hypertension, or morbid obesity, who may have a delay in transit of the tracer arriving after the peak phase.

Regadenoson-stress CMR MPI

Intraindividual comparison of regadenoson- versus adenosine-stress CMR MPI was performed in a prospective study in relation to the caused coronary hyperemia across the range of body sizes seen in a clinical setting. Twenty-eight subjects (12 female, 16 males) were imaged: 43% were obese and 25% had one or more known coronary risk factors. MR imaging with Gd-BOPTA was done first at rest, then during adenosine infusion (140 µg/ kg/min) and 30 min later with regadenoson (0.4 mg over 10 s/ 5 ml bolus). The study showed both vasodilators having a similar efficacy on vasodilation (good agreement between myocardial perfusion reserve (MPR) measured with adenosine and regadenoson ($y = 1.1x - 0.06$, $r = 0.7$)). The studied population would likely not include the broad spectrum of body sizes as might be seen in patients in daily CMR MPI.

Intraindividual comparison of regadenoson versus adenosine was performed in a prospective study to evaluate the effects of vasodilators on CMR-derived ventricular volumes and function in 25 healthy subjects. CMR was performed following adenosine (140 µg/kg/min IV for 6 min) and regadenoson (0.4 mg IV over 10 s) at baseline, immediately following administration, then at 5 min intervals up to 15 min. Peak heart rate was observed early following administration of both adenosine and regadenoson. The increase from baseline to peak heart rate immediately following vasodilator administration was 64 ± 8 to 96 ± 13 bpm for adenosine vs 65 ± 13 to 107 ± 10 bpm for regadenoson. Heart rate returned to baseline by 10 min post-adenosine while remaining elevated at 15 min post-regadenoson. Left ventricular ejection fraction (LVEF) increased immediately following both vasodilators and returned to baseline following adenosine by 10 min, but remained increased at 15 min following regadenoson. Regadenoson resulted in a similar magnitude reduction in both LV end-diastolic volume index (LVEDVi) and LV end-systolic volume index (LVESVi) at 15 min whereas

LVESVi resolved at 15 min following adenosine and LVEDVi remained below baseline values.

Intraindividual comparison was conducted in a prospective study to determine the relative potency of regadenoson (400 μg in bolus), adenosine (140 μg/kg/min over 5 to 6 minutes), and dipyridamole (0.56 mg/kg over 4 minutes) by quantifying stress and rest myocardial perfusion using CMR in 50 young healthy male volunteers. The protocol used in this study as rest-stress imaging is different from currently used protocols: initial rest perfusion CMR imaging, followed twenty minutes later by stress imaging performed at peak vasodilation. Regadenoson produced higher stress myocardial blood flow (MBF) than dipyridamole and adenosine (3.58±0.58 vs. 2.81±0.67 vs. 2.78±0.61 ml/min/g, p=0.0009 and p=0.0008 respectively). Regadenoson had a higher heart rate response than adenosine and dipyridamole (95±11 vs.76±13 vs. 86±12 beats/minute respectively).
When stress MBF was adjusted for heart rate, there were no differences between regadenoson and adenosine (37.8±6 vs. 36.6±4μl/sec/g,), but differences between regadenoson and dipyridamole persisted (37.8 ± 6 vs. 32.6 ± 5μl/sec/g, p=0.03).

Regadenonon-stress MDCT MPI

A Phase 2, multicenter, open-label, randomized, cross-over prospective study was sponsored (Study 3606-CL-2001) to determine agreement rate between regadenoson stress SPECT and regadenoson-stress CT perfusion for detecting the presence of ischemia (defined as 2 or more reversible defects seen visually) in 110 patients with suspected or known CAD referred for one of these diagnostic tests as being clinically indicated. Subjects were randomized to 1 of 2 imaging procedure sequences and to undergo both a rest/stress SPECT and a rest/stress MDCT. Regadenoson was administered as 0.4 mg in a 5 mL IV bolus prior to each stress CT perfusion and stress SPECT procedure.

While regadenoson stress SPECT imaging identified 100 subjects as having 0 – 1 reversible defects (i.e. no ischemia) and 10 subjects as having ≥ 2 reversible defects (i.e. ischemia), regadenoson stress MDCT imaging identified 85 and 25 subjects as having 0 –1 or ≥ 2 reversible defects, respectively. The agreement rate between regadenoson stress SPECT and regadenoson stress MDCT MPI was 87% (95% CI: 77%, 97%).

Suboptimal Exercise Stress Test

In the EXERRT trial the efficacy and safety of regadenoson was evaluated in patients with suboptimal Exercise Stress in an open-label randomized, multi-center, non-inferiority study when regadenoson administered either at 3 minutes during recovery (exercise with regadenoson) or at rest 1 hour later (regadenoson only).

All 1404 patients initially had a baseline SPECT MPI scan at rest in accordance with ASNC 2009 guidelines.

Patients initiated exercise using a standard or modified Bruce protocol. Patients who did not achieve ≥ 85% maximum predicted heart rate (MPHR) and/or ≥ 5 METS (metabolic equivalents), transitioned into a 3-5 minutes walking recovery where during the first 3 minutes of recovery, patients were randomized 1:1.

Therefore, 1147 patients were randomized in two groups: 578 patients from the exercise with regadenoson group and 569 from the regadenoson only group to either 3 minutes recovery (for the exercise with regadenoson group) or at rest 1 hour later (for the regadenoson only group).

Patients from both groups (exercise with regadenoson and regadenoson only) underwent a SPECT Myocardial Perfusion Imaging (MPI) at 60-90 minutes post-regadenoson administration.

The baseline MPI scan at rest, and the MPI scans for the exercise with regadenoson and regadenoson only groups constituted the MPI 1 phase.

Subsequentially, patients from both groups, returned 1-14 days later, to undergo a second stress MPI regadenoson study without exercise.
The baseline MPI scans at rest and those without exercise at 1-14 days later from both groups, constituted the MPI 2 phase.

The images from MPI 1 and MPI 2 were compared for presence or absence of perfusion defects. The level of agreement between the MPI 1 (exercise with regadenoson) and the MPI 2 reads was similar to the level of agreement between MPI 1 (regadenoson only) and MPI 2 reads.

For two patients from the exercise with regadenoson group, a serious cardiac adverse reaction was reported. Upon case review, both patients, experienced ischemic symptoms and ECG changes during exercise or recovery prior to regadenoson administration.
No serious cardiac adverse reactions occurred in patients receiving regadenoson 1 hour following inadequate exercise stress.

Measurement of FFR
For the measurement of FFR, five independent studies have been conducted. A total of 249 patients, who were clinically indicated to undergo coronary angiography with invasive measurement of FFR, received regadenoson, with 88 of those patients receiving regadenoson twice.
FFR was measured after IV infusion of adenosine and IV injection of regadenoson (400 μg). Adenosine was administered first, followed by regadenoson as its hyperaemia may last unpredictably and the measured FFR values were compared.

The most common cardiovascular conditions were patients with a medical history of hypertension, dyslipidemia / hypercholesterolemia, diabetes mellitus, smoking, prior PCI and prior MI.

For FFR measurement, a diagnosis of inducible ischemia was made according to the measurement of FFR of 0.8 (>0.8 represents the absence of inducible ischemia vs ≤ 0.8 representing the presence of inducible ischemia). Adenosine was treated as a gold standard to estimate sensitivity, specificity, and the proportion of accuracy.

Study	**Sensitivity**	**Specificity**	**Classification agreement Cohen's kappa**
Stolker et al. 2015 (n=149)	98%	97%	0.94
van Nunen et al. 2015 (n=98)	98%	95%	0.94

Aminophylline

Aminophylline (100 mg, administered by slow intravenous injection over 60 seconds) injected 1 minute after 400 micrograms regadenoson in subjects undergoing cardiac catheterisation, was shown to shorten the duration of the coronary blood flow response to regadenoson as measured by pulsed- wave Doppler ultrasonography. Aminophylline has been used to attenuate adverse reactions to regadenoson (see section 4.4).

Effect of caffeine
In a study of adult patients undergoing pharmacological stress SPECT MPI with regadenoson, randomized to placebo (n=66) or caffeine (200 mg, n=70 or 400 mg, n=71) administered 90 minutes before the test, caffeine compromised the diagnostic accuracy of detecting reversible perfusion defects ($p<0.001$). There was no statistical difference between 200 mg and 400 mg caffeine with regadenoson. Also, there was no apparent effect of 200 mg or 400 mg of caffeine on regadenoson plasma concentrations.

Safety and tolerability testing
In ADVANCE MPI 1 and ADVANCE MPI 2, the following pre-specified safety and tolerability endpoints comparing regadenoson to adenosine achieved statistical significance: (1) a summed score of both the presence and severity of the symptom groups of flushing, chest pain, and dyspnoea was

lower with regadenoson (0.9 ± 0.03) than with adenosine (1.3 ± 0.05); and (2) the symptom groups of flushing (21% vs 32%), chest pain (28% vs 40%), and 'throat, neck or jaw pain' (7% vs 13%) were less frequent with regadenoson ; the incidence of headache (25% vs 16%) was more frequent with regadenoson .

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with regadenoson in one or more subsets of the paediatric population with myocardial perfusion disturbances (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Regadenoson is administered by intravenous injection for pharmacologic stress MPI. The regadenoson plasma concentration-time profile in healthy volunteers is multi-exponential in nature and best characterised by 3-compartment model. The maximal plasma concentration of regadenoson is achieved within 1 to 4 minutes after injection of regadenoson and parallels the onset of the pharmacodynamic response (see section 5.1). The half-life of this initial phase is approximately 2 to 4 minutes. An intermediate phase follows, with a half-life on average of 30 minutes coinciding with loss of the pharmacodynamic effect. The terminal phase consists of a decline in plasma concentration with a half-life of approximately 2 hours. Within the dose range of 0.003-0.02 mg/kg (or approximately 0.18-1.2 mg) in healthy subjects, clearance, terminal half-life or volume of distribution do not appear dependent upon the dose.

Distribution
Regadenoson is moderately bound to human plasma proteins (25-30%).

Biotransformation
The metabolism of regadenoson is unknown in humans. Incubation with rat, dog, and human liver microsomes as well as human hepatocytes produced no detectable metabolites of regadenoson.
Following intravenous administration of ^{14}C-radiolabeled regadenoson to rats and dogs, most radioactivity (85-96%) was excreted in the form of unchanged regadenoson. These findings indicate that metabolism of regadenoson does not play a major role in the elimination of regadenoson.

Elimination
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.

Multiple injections
Up to three consecutive injections of regadenoson (100 and 200 μg) have been tested in healthy volunteers, and two consecutive doses of 400 μg in healthy volunteers, as well as in patients assessed for FFR. Transient dose dependent increases in heart rate occurred following administration of each dose of regadenoson, whereas no consistent dose-related effect on systolic blood pressure was observed. Mean plasma concentrations increased in a dose-related manner and by successive doses as observed in healthy volunteers.
Special populations
A population pharmacokinetic analysis including data from subjects and patients demonstrated that regadenoson clearance decreases in parallel with a reduction in creatinine clearance (CLcr) and increases with increased body weight. Age, gender, and race have minimal effects on the pharmacokinetics of regadenoson.

Renal impairment
The disposition of regadenoson was studied in 18 subjects with various degrees of renal function and in 6 healthy subjects. With increasing renal impairment, from mild (CLcr 50 to < 80 ml/min) to moderate (CLcr 30 to < 50 ml/min) to severe renal impairment (CLcr < 30 ml/min), the fraction of regadenoson excreted unchanged in urine and the renal clearance decreased, resulting in increased elimination half-

lives and AUC values compared to healthy subjects (CLcr ≥ 80 ml/min). However, the maximum observed plasma concentrations as well as volumes of distribution estimates were similar across the groups. The plasma concentration-time profiles were not significantly altered in the early stages after dosing when most pharmacologic effects are observed. No dose adjustment is needed in patients with renal impairment.

The pharmacokinetics of regadenoson in patients on dialysis has not been assessed.

Hepatic impairment
Greater than 55% of the regadenoson dose is excreted unchanged in the urine and factors that decrease clearance do not affect the plasma concentration in the early stages after dosing when clinically meaningful pharmacologic effects are observed. The pharmacokinetic parameters of regadenoson have not been specifically evaluated in those with varying degrees of hepatic impairment. However, post-hoc analysis of data from the two Phase 3 clinical trials showed that the pharmacokinetics of regadenoson were not affected in a small subset of patients with laboratory values suggestive of impaired hepatic function (2.5-fold transaminase elevation or 1.5-fold elevation of serum bilirubin or prothrombin time). No dose adjustment is needed in patients with hepatic impairment.

Elderly patients
Based on a population pharmacokinetic analysis, age has a minor influence on the pharmacokinetics of regadenoson. No dose adjustment is needed in elderly patients.

Paediatric population
The pharmacokinetic parameters of regadenoson have not yet been studied in the paediatric population (< 18 years).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity, or embryo-fetal development. Signs of maternal and fetal toxicity were seen in rats and rabbits (reduced fetal weights, delays in ossification [rats], reduced litter size and number of live fetuses [rabbits]), but not teratogenicity. Fetal toxicity was noted following repeated daily administration of regadenoson, but at doses sufficiently in excess of the recommended human dose. Fertility and pre- and post-natal studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dihydrate
Sodium dihydrogen phosphate monohydrate
Propylene glycol
Disodium edetate
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 ml solution in a single use Type 1 glass vial with (butyl) rubber stopper and aluminium over-seal.

Pack size of 1.

6.6 Special precautions for disposal and other handling

This medicinal product should be inspected visually for particulate matter and discolouration prior to administration.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/643/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06/09/2010
Date of latest renewal: 24/04/2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Millmount Healthcare Limited,
Block 7, City North Business Campus,
Stamullen, Co Meath, K32 YD60
Ireland

Haupt Pharma Wolfratshausen GmbH
Pfaffenrieder Str. 5
D-82515 Wolfratshausen,
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rapiscan 400 microgram solution for injection
regadenoson

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 5 ml vial contains 400 micrograms regadenoson (80 micrograms/ml).

3. LIST OF EXCIPIENTS

Excipients: Disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, propylene glycol, disodium edetate, water for injections

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use product only in medical facilities with cardiac monitoring and resuscitation equipment.
For diagnostic use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/643/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Rapiscan 400 microgram solution for injection
Regadenoson
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 micrograms

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Rapiscan 400 microgram solution for injection
Regadenoson

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.

If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Rapiscan is and what it is used for

Rapiscan contains the active substance regadenoson**.** This belongs to a group of medicines called 'coronary vasodilators'. It makes the heart arteries expand and heart rate increase. This makes more blood flow to the muscles of the heart.

This medicine is for diagnostic use only.

Rapiscan is used in a type of heart scan in adults called 'myocardial perfusion imaging'.

The scan uses a diagnostic agent to create images. These images show how well blood flows to the muscles of the heart. Usually, exercise on a treadmill is used to put the heart under stress before a scan. During the exercise, a small amount of the diagnostic agent is injected into the body, often into a vein in the hand. Images are then taken of the heart. The doctor can then see if the heart muscles are getting enough blood flow when it is under stress.
If you are unable to exercise enough to reach sufficient stress to the heart, Rapiscan will be injected to provide a stress of similar amplitude to the heart to increase the blood flow.
Rapiscan is also used during catheterisation and imaging arteries of the heart (invasive coronary angiography) to expand the arteries of the heart to measure the difference in pressure, caused by a narrowing within one or more arteries. During cardiac catheterisation, a long thin tube called a catheter is inserted either through your femoral or radial artery and threaded through your blood vessels to your heart. The doctor performing the catheterisation may also want to measure the difference in pressure (fractional flow reserve) due to a narrowing detected in one or more arteries of the heart.

2. What you need to know before you are given <u>Rapiscan</u>

Do not take Rapiscan:

- if you have slow heart rate (high degree heart block or sinus node disease), and don't have a pacemaker fitted.
- if you have chest pain that occurs unpredictably (unstable angina) and that has not improved after treatment.
- if you have low blood pressure (hypotension).
- if you have heart failure.

- if you are allergic to regadenoson or any of the other ingredients of Rapiscan listed in section 6 of this leaflet.

Talk to your doctor or nurse before taking Rapiscan
Your doctor needs to know before you are given Rapiscan:
- if you have had a **recent serious heart problem** (for example a heart attack or abnormal heart rhythms).
- if you have a heart rhythm where your heartbeat is very fast or uneven (atrial fibrillation or atrial flutter)
- if you have high blood pressure that is not controlled, especially if this has been accompanied by recent episodes of nose bleed, headache or blurred or double vision.
- if you have had episodes of mini strokes (called transient ischaemic attacks)
- if you have a heart rhythm disorder called **long QT syndrome**.
- if you have episodes of **heart block** (which can slow the heart down) or a **very slow heart rate**.
- if you have any **heart** or **blood vessel condition**, particularly one that **gets worse** when your blood pressure decreases. These include low blood volume (caused, for example, by severe diarrhoea or dehydration or taking water pills), inflammation around the heart (pericarditis) and some forms of heart valve or artery disease (for example, aortic or mitral stenosis).
- if you have a condition that causes fits (seizures), such as epilepsy, or if you have ever had fits.
- if you have **asthma** or **lung disease**.

If any of these apply to you, **tell your doctor before you are given the injection.**

Children and adolescents
Rapiscan should not be used in children and adolescents below the age of 18 years.

Other medicines and Rapiscan
Please tell your doctor if you are taking or have recently taken any other medicines including medicines obtained without prescription.

Particular care should be taken with the following medicines:
- **theophylline**, a medicine used to treat asthma and other lung diseases, **must not be used for at least 12 hours before** you are given Rapiscan because it can block the effect of Rapiscan.
- **dipyridamole**, a medicine used to prevent blood clots, **must not be used for at least two days before** you are given Rapiscan because it can change the effect of Rapiscan.

Rapiscan with food and drink
Do not eat food or have drinks containing caffeine (for example, tea, coffee, cocoa, cola or chocolate) for at least 12 hours before you are given Rapiscan. This is because caffeine can interfere with the effect of Rapiscan.

Pregnancy and breast-feeding
Before you are given Rapiscan, tell your doctor:
- if **you are pregnant**, think you are pregnant or planning to have a baby. There is no adequate information on the use of Rapiscan in pregnant women. Harmful effects have been seen in animal studies but it is not known if there is a risk to humans. Your doctor will only give you Rapiscan if it is clearly necessary.
- if **you are breast-feeding**. It is not known whether Rapiscan can pass into breast milk and will only be given to you if your doctor thinks it is necessary. You should avoid breast-feeding for at least 10 hours after you are given Rapiscan.

Ask your doctor for advice before using any medicine.

Driving and using machines
Rapiscan may make you feel dizzy. It may cause other symptoms (headache or shortness of breath) that could affect your ability to drive or use machinery. These effects usually do not last longer than 30 minutes. Do not drive or operate machinery until these effects have improved.

Rapiscan contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose. After you have been given Rapiscan, you will be given an injection of sodium chloride 9 mg/ml (0.9%) solution which contains 45 mg of sodium. To be taken into consideration if you are on a controlled sodium diet.

3. How Rapiscan is given

Rapiscan is injected by a healthcare professional (a doctor, nurse or medical technician) in a medical facility where your heart and blood pressure can be monitored. It is injected directly into a vein, as a single dose of 400 micrograms in a 5 ml solution – the injection will take about 10 seconds to complete. The dose injected does not depend on your weight.

You will also be given an injection of sodium chloride 9 mg/ml (0.9%) solution (5 ml), and an injection of a small amount of a diagnostic agent.
When you are given Rapiscan, your heart rate will increase quickly. Your heart rate and blood pressure will be monitored.

After the Rapiscan injection you will need to sit or lie down until your heart rate and blood pressure return to your normal levels. The doctor, nurse or medical technician will let you know when you can stand up.

A scan of your heart will be made after enough time has passed to allow the diagnostic agent to reach the heart muscle.
During catheterisation of the arteries of the heart, your doctor may measure the pressure difference (also known as fractional flow reserve – FFR) due to a narrowing in one or more arteries of the heart.

If deemed necessary, a second dose of 400 micrograms can be injected at least 10 minutes after the first dose for such pressure difference measurement during the same catheterization procedure. Heart rate and blood pressure will be monitored during the entire procedure.

If you are given more Rapiscan than you should
Some people have had flushing, dizziness and increased heart rate when they have been given too much Rapiscan. If your doctor thinks that you are having severe side effects, or the effects of Rapiscan are lasting too long, they may give you an injection of a medicine called aminophylline that reduces these effects.

4. Possible side effects

Like all medicines, Rapiscan can cause side effects, although not everybody gets them.

The side effects are usually mild. They normally start soon after the Rapiscan injection and are **usually over within 30 minutes**. They don't usually need any treatment.

More serious side effects include:
- sudden stopping of the heart or damage to the heart, heart block (a disorder of the heart's electrical signal, where the signal cannot pass from the upper to the lower chambers), rapid heart beat
- low blood pressure which may result in fainting or mini strokes (including weakness of the face or an inability to speak). Rarely, Rapiscan can cause a stroke (also known as a cerebrovascular accident).
- an allergic reaction which can cause rash, wheals/weals, swelling under the skin near the eyes or throat, throat tightness, and difficulty in breathing may occur immediately or have delayed onset after Rapiscan injection

Tell your doctor straight away if you think you are having severe side effects. Your doctor may then give you an injection of a medicine called aminophylline that reduces these effects.

Very common
(may affect more than 1 in 10 people)
- headache, dizziness
- shortness of breath
- chest pain
- changes in heart tracing tests (electrocardiogram)
- flushing
- discomfort in the stomach

Common
(may affect up to 1 in 10 people)
- heart pain (angina), abnormal heart rhythms, rapid heart beat, feeling the heart skipping a beat, fluttering, or beating too hard or fast (palpitations)
- low blood pressure
- throat tightness, throat irritation, cough
- being sick (vomiting), feeling sick (nausea)
- feeling unwell or weak
- excessive sweating
- pain in the back, arms, legs, neck or jaw
- discomfort in the bones and muscles
- pins and needles, reduced sensation, taste changes
- discomfort in the mouth

Uncommon
(may affect up to 1 in 100)
- sudden stopping of the heart or damage to the heart, heart block (a disorder of the heart's electrical signal, where the signal cannot pass from the upper to the lower chambers), slow heart beat
- fits, fainting, mini strokes (including weakness of the face or an inability to speak), reduced responsiveness (which may include a comatose state), trembling, sleepiness
- an allergic reaction which can cause rash, wheals/weals, swelling under the skin near the eyes or throat, throat tightness, difficulty breathing
- wheezing
- rapid breathing
- high blood pressure, paleness, cold extremities
- blurred vision, eye pain
- anxiety, difficulty sleeping
- ringing in the ears
- bloating, diarrhoea, involuntary loss of faeces
- redness of the skin
- pain in the joints
- pain or discomfort around the area injected, body pain

Not known
(frequency cannot be estimated from the available data)
- difficulty in breathing (bronchospasm)
- respiratory arrest

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rapiscan

Keep out of the reach and sight of children.

Do not use Rapiscan after the expiry date which is stated on the vial and carton after EXP. This medicine does not require any special storage conditions.

Rapiscan must not be used if the solution if it is discoloured or particulate matter is present.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment. The healthcare professionals will be responsible for the storage and disposal of this medicinal product.

6. Contents of the pack and further information

What Rapiscan contains
The active substance in Rapiscan is regadenoson. Each 5 ml vial of Rapiscan contains 400 micrograms of regadenoson.

The other ingredients are: disodium edetate, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, propylene glycol, water for injections.

What Rapiscan looks like and contents of the pack
Rapiscan solution for injection is a clear, colourless solution with no particles visible. Rapiscan is supplied in a carton containing a single use 5 ml glass vial with a rubber stopper and aluminium sealed cap.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

GE Healthcare AS
Nycoveien 1
NO-0485 Oslo
Norway

Manufacturer:

Millmount Healthcare Limited
Block 7, City North Business Campus,
Stamullen, Co Meath, K32 YD60 Ireland

Haupt Pharma Wolfratshausen GmbH
Pfaffenrieder Str. 5
D-82515 Wolfratshausen,
Germany

This leaflet was last revised in MM/YYYY

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Rapiscan should be administered as a rapid, 10-second injection into a peripheral vein using a 22-gauge or larger catheter or needle.

5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection should be administered immediately after the injection of Rapiscan.

The diagnostic agent for the myocardial perfusion imaging agent should be administered 10-20 seconds after the sodium chloride 9 mg/ml (0.9%) solution for injection. The diagnostic agent may be injected directly into the same catheter as Rapiscan.

For the measurement of FFR, Rapiscan should be administered as a rapid, 10-second injection into a peripheral vein using a 22-gauge or larger catheter or needle. 10 mL of sodium chloride 9 mg/ml (0.9%) solution for injection should be administered immediately after the injection of Rapiscan. Standard catheterisation and FFR measurement techniques are to be followed, and FFR should be measured as the lowest value of Pd/Pa achieved during steady state maximum hyperemia.

If deemed necessary, a second dose of 400 micrograms can be injected at least 10 minutes after the first dose for FFR measurement during the same catheterization procedure.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

This medicinal product should be inspected visually for particulate matter and discolouration prior to administration.

Any unused product or waste material should be disposed of in accordance with local requirements.

For further information, please refer to the complete Summary of Product Characteristics.