

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 as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress.

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

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.

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.

- 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 radiopharmaceutical 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 radiopharmaceutical may be injected directly into the same catheter as Rapiscan.

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

Rapiscan 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. Rapiscan 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 Rapiscan but should not be used solely for the purpose of terminating a seizure induced by Rapiscan.

Myocardial ischaemia

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

Rapiscan should be used in caution in patients with recent myocardial infarction. Clinical trials conducted with regadenoson excluded patients with recent (within 3 months) 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

Rapiscan 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 Rapiscan administration until blood pressure is well controlled

Combination with exercise

Use of Rapiscan 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

Rapiscan 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 Rapiscan 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 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 Rapiscan is not recommended.

Atrial fibrillation or flutter

Rapiscan 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 Rapiscan.

Bronchoconstriction

Adenosine receptor agonists, including Rapiscan, 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 Rapiscan 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 than 1 mmol sodium (23 mg) per dose. However, the injection of sodium chloride 9 mg/ml (0.9%) solution given after Rapiscan 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

No studies of interaction with other medicinal products have been performed.

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 Rapiscan administration (see section 4.2).

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 Rapiscan (see section 4.4).

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 Rapiscan administration (see section 4.2).

Cardioactive medicinal products

In clinical studies, Rapiscan 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 Rapiscan.

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 μ M. 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 Rapiscan 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. Rapiscan 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 Rapiscan administration taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. If Rapiscan 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 Rapiscan administration.

Fertility

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

4.7 Effects on ability to drive and use machines

Rapiscan 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 Rapiscan. Therefore, Rapiscan 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 Rapiscan in clinical trials were mild, transient (usually resolving within 30 minutes after receiving Rapiscan), 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%).

Rapiscan 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 Rapiscan but should not be used solely for the purpose of terminating a seizure induced by Rapiscan (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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ to $< 1/1,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<i>Immune system disorders:</i>	
Uncommon	Hypersensitivity reactions including: Rash, urticaria, angioedema, anaphylaxis
<i>Psychiatric disorders:</i>	
Uncommon	Anxiety, insomnia
<i>Nervous system disorders:</i>	
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
<i>Eye disorders:</i>	
Uncommon	Vision blurred, eye pain
<i>Ear and labyrinth disorders:</i>	
Uncommon	Tinnitus
<i>Cardiac disorders:</i>	
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
<i>Vascular disorders:</i>	
Very common	Flushing
Common	Hypotension
Uncommon	Hypertension, pallor, peripheral coldness
<i>Respiratory, thoracic and mediastinal disorders:</i>	
Very common	Dyspnoea
Common	Throat tightness, throat irritation, cough
Uncommon	Tachypnoea, wheezing
Not known	Bronchospasm, Respiratory arrest
<i>Gastrointestinal disorders:</i>	
Very common	Gastrointestinal discomfort
Common	Vomiting, nausea, oral discomfort
Uncommon	Abdominal distension, diarrhoea, faecal incontinence
<i>Skin and subcutaneous tissue disorders:</i>	
Common	Hyperhidrosis
Uncommon	Erythema
<i>Musculoskeletal and connective tissue disorders:</i>	
Common	Back, neck or jaw pain, pain in extremity, musculoskeletal discomfort
Uncommon	Arthralgia
<i>General disorders and administration site conditions:</i>	
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 Rapiscan (see section 4.4).

Sinoatrial and atrioventricular nodal block

Adenosine receptor agonists, including Rapiscan, 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 Rapiscan administration; transient second degree AV block with one dropped beat was observed in one

patient receiving Rapiscan. In postmarketing experience, third degree heart block and asystole have been reported within minutes of Rapiscan administration.

Hypotension

Adenosine receptor agonists, including Rapiscan 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 Rapiscan 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 Rapiscan 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 $< 1\%$).

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 Rapiscan (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 ($K_i \approx 1.3$ μ M) for the A_{2A} adenosine receptor, with at least 10-fold lower affinity for the A₁ adenosine receptor ($K_i > 16.5$ μ M), and very low, if any, affinity for the A_{2B} and A₃ 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 EC₅₀ 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 (A1-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 Rapiscan (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 Rapiscan administration is therefore greater in areas perfused by normal relative to stenosed arteries.

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 Rapiscan. 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 Rapiscan 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 A2B and A3 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 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. In the first study in 49 patients with moderate to severe COPD, the rate of FEV₁ reduction $> 15\%$ from baseline was 12% and 6% following Rapiscan 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 FEV₁ reduction $> 15\%$ from baseline was the same (4%) following both Rapiscan 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 FEV₁ 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 Rapiscan and placebo dosing, respectively. In the first and second studies, dyspnoea was reported as an adverse reaction following Rapiscan 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 Rapiscan (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 Rapiscan and placebo. Dyspnoea did not correlate with a decrease in FEV₁.

Clinical efficacy and safety

Clinical studies have demonstrated the efficacy and safety of Rapiscan in patients indicated for pharmacologic stress radionuclide MPI.

The efficacy and safety of Rapiscan 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 radionuclide gated SPECT (single photon emission computed tomography) imaging protocol. After the initial scan, patients were randomised to either Rapiscan or adenosine, and received a second stress scan with the same radionuclide imaging 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%).

Image agreement

Comparison of the images obtained with Rapiscan 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 Rapiscan 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 Rapiscan 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 Rapiscan 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 Rapiscan 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 (\pm SE)	61 \pm 3%	64 \pm 4%	62 \pm 3%
Number of Patients (n)	372	259	631
Adenosine – Rapiscan Agreement Rate (\pm SE)	62 \pm 2%	63 \pm 3%	63 \pm 2%
Number of Patients (n)	741	499	1,240
Rate Difference (Rapiscan – Adenosine) (\pm SE)	1 \pm 4%	-1 \pm 5%	0 \pm 3%
95% Confidence Interval	-7.5, 9.2%	-11.2, 8.7%	-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.

Effect of caffeine

In a study of adult patients undergoing pharmacological stress radionuclide MPI with Rapiscan, 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 Rapiscan. 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 Rapsican 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 Rapsican (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 Rapsican; the incidence of headache (25% vs 16%) was more frequent with Rapsican.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Rapsican 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

Rapsican is administered by intravenous injection. 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 Rapsican 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.

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 (CL_{Cr}) 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 (CL_{Cr} 50 to < 80 ml/min) to moderate (CL_{Cr} 30 to < 50 ml/min) to severe renal impairment (CL_{Cr} < 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 (CL_{Cr} 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**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR <THE CONDITIONAL MARKETING AUTHORISATION> <THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES>>**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AndersonBrecon (UK) Ltd
Wye Valley Business Park
Hay-on-Wye, Hereford
HR3 5PG, United Kingdom

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 marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

**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.

In this leaflet:

1. What Rapiscan is and what it is used for
2. What you need to know before you are given Rapiscan
3. How Rapiscan is given
4. Possible side effects
5. How to store Rapiscan
6. Contents of the pack and other information

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 radioactive substance called a 'radiopharmaceutical' 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 radiopharmaceutical 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.

It is used in patients who are unable to exercise enough for the scan

2. What you need to know before you are given rapiscan

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 pharmacist 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 radioactive substance (radiopharmaceutical).

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 radiopharmaceutical to reach the heart muscle.

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 side effects

(affects more than 1 user in 10)

- headache, dizziness
- shortness of breath
- chest pain
- changes in heart tracing tests (electrocardiogram)
- flushing
- discomfort in the stomach

Common side effects

(affects 1 to 10 users in 100)

- 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 side effects

(affects 1 to 10 users in 1,000)

- 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:

AndersonBrecon (UK) Ltd
Wye Valley Business Park
Hay-on-Wye, Hereford
HR3 5PG, United Kingdom

This leaflet was last approved in

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

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 radiopharmaceutical 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 radiopharmaceutical may be injected directly into the same catheter as Rapiscan.

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 enclosed with the pack.