HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

20 November 2013

RAPISCAN 400 micrograms, solution for injection

B/1 vial of 5 ml (CIP: 34009 584 963 9 4)

Applicant: COVIDIEN IMAGING FRANCE

INN	**regadenoson**
ATC Code (2012)	**C01EB21 (other cardiac preparations)**
Reason for the request	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"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."**

Actual Benefit	**The actual benefit of RAPISCAN is low.**
Improvement in Actual Benefit	**RAPISCAN, as a pharmacological stress agent for radionuclide myocardial perfusion imaging in patients with coronary disease unable to undergo adequate exercise stress, does not provide any improvement in actual benefit (IAB V, non-existent).**
Therapeutic use	**RAPISCAN is a new pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 6 September 2010
Prescribing and dispensing conditions	List I Medicinal product for hospital use only.

ATC Classification	2013	
	C	Cardiovascular system
	C01	Cardiac therapy
	C01E	Other cardiac preparations
	C01EB	Other cardiac preparations
	C01EB21	regadenoson

02 BACKGROUND

The applicant is requesting the inclusion of RAPISCAN on the list of proprietary medicinal products approved for hospital use.

RAPISCAN is a selective vasodilator of the A2A-AdoR receptors present on the walls of the blood vessels of the heart.

03 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."

04 DOSAGE

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

Posology
The recommended dose of RAPISCAN is a single injection of 400 micrograms of 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 of the SPC).

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

Aminophylline may be used to attenuate severe and/or persistent adverse reactions to RAPISCAN (see section 4.4 of the SPC).

RAPISCAN causes a rapid increase in heart rate (see sections 4.4 and 5.1 of the SPC). 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 RAPISCAN 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 of the SPC).

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

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

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."

05 THERAPEUTIC NEED

Radionuclide myocardial perfusion imaging is an cardiac examination exploration performed in nuclear imaging departments enabling the screening, diagnosis, assessment or monitoring of a coronary event. The technique evaluates the perfusion of the myocardium and enables ventricular contractility during major (myocardial infarction, myocardial ischaemia) or minor (revascularisation, unstable angina) coronary events to be assessed. For a decade, the standard technique has been radionuclide myocardial imaging coupled with an electrocardiogram (SPECT; CT scintigraphy) using a radiopharmaceutical isotope as a tracer (thallium^{201} chloride or technetium^{99m}).

The image obtained enables the radiation emitted by the isotope to be visualised. In a single acquisition of images, radionuclide myocardial perfusion provides information on the state of regional vascularisation of the heart muscle, the extent of the potential damage and details of left ventricular function (LVEF).
Using radionuclide myocardial perfusion imaging, SPECT enables the screening of heart disease and helps in its diagnosis. This examination also provides prognosis information on the coronary risk from a single prognostic assessment, based on the combination of clinical, biological, ECG and ultrasound parameters.[1]

The MPI results are dependent on the quality of the stress test.[2] This stress test can be carried out through physical exercise (running on a treadmill or pedalling on a bicycle). During this physical exercise stress test, the appropriate heart rate level to carry out a satisfactory test must be at least 85% of the maximum theoretical rate. However, 40% to 50% of patients are not able to achieve this heart rate threshold, depending on their clinical background.
Therefore, when a physical stress test is unsatisfactory, contraindicated, or impossible for the patient, myocardial ischaemia is provoked by the administration of a pharmacological stress agent. Within the context of this second-line indication, adenosine (ADENOSCAN) or dipyridamole (PERSANTIN), administered via injection, are used. In cases of contraindication or intolerance to one of these products, dobutamine may be used.[3]

06 CLINICALLY RELEVANT COMPARATORS

Pharmacological stress agents used for patients who cannot perform a satisfactory stress test during coronary diagnostic investigations are as follows (Table 1):
- adenosine (ADENOSCAN);
- dipyridamole (PERSANTIN).

[1] Shaw L, Iskandrian A. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol 2004; 11: 171-85
[2] Manrique A et al. Recommendations for the performance and interpretation of myocardial perfusion tomoscintigraphy. Arch Mal Coeur Vaiss. 2003; 96(6): 695-711.
[3] Johnson SG, Peters S. Advances in Pharmacologic Stress Agents: Focus on Regadenoson. J Nucl Med Technol 2010; 38:163-171.

Table 1: comparator medicinal products

INN Proprietary medicinal product *Company*	Indication	AB	IAB	Date of opinion	Reimbursed
Adenosine ADENOSCAN *SANOFI - AVENTIS*	Intravenous (IV) ADENOSCAN is a coronary vasodilator for use in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate.	Opinion not available			Approved for hospital use
Dipyridamole PERSANTIN **10 mg/2 ml, solution for injection** ***BOEHRINGER INGELHEIM***	Cardiovascular function investigations: the detection of myocardial ischaemia is carried out by a cardiac stress test in conjunction or not with radionuclide myocardial perfusion imaging. The use of injectable PERSANTIN is indicated when the stress test cannot be carried out or is not contributory (left branch block). Furthermore, the radionuclide imaging test with injectable PERSANTIN can be potentially combined with a stress test with different protocols in order to optimise the detection of ischaemia.	Low	Not qualified	10 May 2006	Approved for hospital use

◗ Conclusion

ADENOSCAN and PERSANTIN are clinically relevant comparators.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

On 10 April 2008, this medicinal product was awarded Marketing Authorisation in the USA in the following indication: "*LEXISCAN is a pharmacological stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.*"
RAPISCAN is marketed by Astellas US under the name LEXISCAN in the USA.
RAPISCAN has had European Marketing Authorisation (centralised procedure) since 6 September 2010.

08 ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy and safety of regadenoson is based on two phase III studies (studies CVT 5131[4] and CVT 5132[5]).
The methodology of both of these studies versus adenosine is similar and is presented below.

08.1 Efficacy

Methodology

Both studies (CVT 5131 and CVT 5132) were randomised, multicentre, double-blind trials versus an active comparator (adenosine). Their aim was to compare the efficacy and safety of regadenoson with those of adenosine in patients with known or suspected coronary disease and who underwent MPI with a pharmacological stress agent.
They are both non-inferiority studies.

Inclusion and non-inclusion criteria

The main inclusion criteria were:
- men or women aged 18 years and above;
- patients for whom a MPI with a pharmacological stress agent was clinically indicated.

The main non-inclusion criteria were:
- a history of coronary revascularisation (percutaneous coronary intervention, coronary artery bypass surgery and transmyocardial revascularisation) in the six months prior to inclusion;
- a documented history of acute myocardial infarction or unstable angina in the three months prior to inclusion;
- a history of unmanaged, severe ventricular arrhythmia.

[4] Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE, and ADVANCE MPI Investigators. Effects of age, gender, obesity and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging; Integrated ADVANCE-MPI trial results. JACC Cardiovascular Imaging 2008; 1: 307–16.
[5] Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC, Lieu H, Mahmarian JJ, Olmsted A, Underwood SR, Vitola J, Wang W, and ADVANCE MPI Investigators. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. J Nucl Cardiol 2007; 14: 645-58.

Treatments

These studies were organised into two stages:

Selection

Each patient included had an initial MPI-SPECT investigation (^{201}thallium and ^{99m}technetium were used for these investigations) with adenosine administered via IV infusion at a dose of 0.14 mg/kg/min for 6 minutes.

Randomisation

In cases where the images obtained at rest and under stress during the initial stress test with adenosine were of good quality, the patients were randomised, at a ratio of 2:1, to have a second stress test between 1 and 30 days after the initial test:

- • Regadenoson group (in practice the adenosine-regadenoson arm): the second examination was performed with administration of regadenoson, 400 µg via IV bolus, followed immediately by 5 ml of 0.9% sodium chloride;
- • Adenosine group (in practice the adenosine-adenosine arm): the second examination was performed using an IV infusion of adenosine at a dosage of 0.14 mg/kg/min for 6 minutes.

Endpoints

Primary efficacy endpoint:

The primary diagnostic efficacy endpoint was the correspondence rate of the images obtained with regadenoson compared with adenosine for the number of segments with reversible infusion defects, determined based on an evaluation of the images by three independent experts interpreting them "blind".

The correspondence rate used for the non-inferiority test was based on the number of segments with reversible infusion defects, using a 17 segments model. The number of ischaemic segments with reversible defects corresponds to an estimation of the extent of the ischaemia. These measurements are considered as being appropriate for the evaluation of diagnostic efficacy and are recommended by the American Heart Association.[6]

Each independent reading defined a score for the 17 anatomical segments of the images obtained at rest and under stress using the following scale:

- 0 = normal
- 1 = mild reduction / equivocal
- 2 = moderate reduction
- 3 = severe reduction
- 4 = no absorption

The calculation of the median number of segments with reversible anomalies across the three readings was defined as:

- 0-1 segments with reversible infusion defects = no ischaemia;
- 2-4 segments with reversible infusion defects = mild to moderate ischaemia;
- 5-17 segments with reversible infusion defects = severe ischaemia.

The non-inferiority of regadenoson compared with adenosine was established if the lower limit of the 95% confidence interval (95% CI) of the difference between the correspondence rates (adenosine-regadenoson arm – adenosine-adenosine arm) was above the pre-established limit of -13.3%.

[6] Cerqueira MD, Weissman NJ, Dilsizian V et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002; 105: 539-542.

Secondary endpoints included:

Safety was compared between the two groups. During the two studies, in instances of non-inferiority of regadenoson *versus* adenosine for the primary endpoint, seven hypotheses relating to the safety of regadenoson *versus* adenosine were scheduled, according to a pre-specified hierarchical order. The test sequence was run until the first non-significant result was achieved. In cases of discontinuation of the series of hierarchical tests, the analyses subsequently carried out were considered as non-demonstrative.
The seven comparative safety endpoints were, in order:

1. score for combined "flushing, chest pain, dyspnoea" symptoms (0 = none; 1 = low; 2 = moderate; 3 = severe) occurring during the 30 minutes after administration of the stress agent;
2. the incidence of "flushing", "chest pain", "dyspnoea", "headaches", "pain to the throat, neck and jaw", "gastrointestinal discomfort" and "dizziness/vertigo" symptoms, occurring during the 30 minutes after administration of the stress agent;
3. the incidence of a reduction in systolic blood pressure (SBP) > 25 mmHg compared with baseline, occurring between 2 and 45 minutes after the administration of the stress agent;
4. the response of patients to the question: "How did you feel during the test?" (1: comfortable to 4: extremely uncomfortable);
5. adverse events (AE) where the incidence was greater than at least 1% between the groups (with the exception of AEs that took into account steps 1 and 2), serious adverse events (SAE) where the incidence was greater than at least 1% between the groups;
6. the response of patients to the question: "How did you feel during the test in comparison with the first test?" (1: a lot better to 4: much worse);
7. the incidence of 2nd degree or complete atrio-ventricular blocks on the ECG.

Distribution of participants

In total, 2,018 patients were randomised in the CVT 5131 and CVT 5132 studies, including:
- 1,339 patients who received regadenoson during the second stress test [adenosine-regadenoson arm] (CVT 5131: 820 patients; CVT 5132: 519 patients),
- 679 patients who received adenosine during the second stress test [adenosine-adenosine arm] (CVT 5131: 411 patients; CVT 5132: 268 patients).

Table 2: studies CVT 5131 and CVT 5132 – patient distribution

Study	**Patients randomised (n)**		**Assessable patients (n)**	
	regadenoson	**adenosine**	**regadenoson**	**adenosine**
CVT 5131	820	411	741	372
Total	1231		1113	
CVT 5132	519	268	499	259
Total	787		758	
2 pooled studies	1,339	679	1,240	631
Total	2,018		1,871	

Patients in the "no ischaemia" category (0-1 segments with reversible ischaemia) were notably excluded from the efficacy analysis.

The assessable population for the primary efficacy analysis was 1,871 patients, including 1,240 patients who received regadenoson and 631 who received adenosine.

Patient characteristics

The demographic and disease characteristics were homogeneous in the treatment groups.
The majority of patients were male (69%; 1294/1871) and Caucasian (75%; 1407/1871). The median age at inclusion was 66 years (26-93 years).
The most commonly reported cardiovascular histories at inclusion were: coronary disease (77%; 1,441/1,871), hypertension (81%; 1,514/1,871), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), or implantation of a stent (51%, 950/1,871), angina (63%, 1,176/1,871), history of myocardial infarction (41%, 764/1,871) or arrhythmia (33%, 607/1,871). In addition, 32% (607/1,871) of patients had diabetes, and 69% (1,287/1,871) had heart failure.

Table 3: Studies CVT 5131 and CVT 5132 – Baseline patient characteristics

Characteristics	Regadenoson n= 1,240	Adenosine n= 631	All n= 1,871
Age, median (range)	66 (27-93)	65 (26-91)	66 (26-93)
Male, n (%)	864 (70%)	430 (68%)	1,294 (69%)
Caucasian, n (%)	935 (75%)	472 (75%)	1,407 (75%)
Weight, median kg, (range)	82 (42-161)	83 (44-147)	82 (42-161)
BMI, median kg/m^2, (range)	29 (16-57)	28 (18-59)	29 (16-59)
Left ventricular ejection fraction ≥ 35%, n (%)	1,084 (87%)	553 (88%)	1,637 (87%)
Cardiovascular history, n (%)			
Coronary disease	966 (78%)	475 (75%)	1,441 (77%)
Hypertension	1,012 (82%)	502 (80%)	1,514 (81%)
Angina	789 (64%)	387 (61%)	1,176 (63%)
Coronary artery bypass graft, percutaneous coronary intervention, implantation of a stent	627 (51%)	323 (51%)	950 (51%)
Myocardial infarction	494 (40%)	270 (43%)	764 (41%)
Arrhythmia	418 (34%)	204 (32%)	662 (33%)
Diabetes	394 (32%)	213 (34%)	607 (32%)
Heart failure	226 (18%)	109 (17%)	335 (18%)

Results

Correspondence rate of images

During studies CVT 5131 and CVT 5132, the correspondence rates (Table 4) were:

- 62% pour for the regadenoson arm and 61% for the adenosine arm in study CVT 5131,
- 63% for the regadenoson arm and 64% for the adenosine arm in study CVT 5132.

The difference in correspondence rates (regadenoson – adenosine) was:

- 1±4% (95% CI: [-7.5; 9.2]) in study CVT 5131,
- -1± 5% (95% CI: [-11.2; 8.7]) in study CVT 5132.

Table 4: Studies CVT 5131 and CVT 5132 – Correspondence rates

	CVT 5131 n = 1,113	CVT 5132 n = 758	Combined studies n = 1,871
Adenosine – adenosine correspondence rate (± SD), number of patients (n)	61 ± 3% (372)	64 ±4% (259)	62 ± 3% (631)
Adenosine – regadenoson correspondence rate (± SD), number of patients (n)	62 ± 2% (741)	63 ± 3% (499)	63 ± 2% (1,240)
Difference between the rates (regadenoson – adenosine) (± SD) 95% confidence interval	1 ± 4% (-7.5; 9.2%)	-1 ± 5% (-11.2; 8.7%)	0 ± 3% (-6.2; 6.8%)

In both studies, the lower limit of the 95% confidence interval of the difference in the correspondence rates between the two treatments (regadenoson arm – adenosine arm) was above the pre-defined limit of -13.3%; regadenoson was thus non-inferior to adenosine in terms of the correspondence of images for the evaluation of the extent of reversible myocardial infusion abnormalities.

The pooled analysis for the two studies reported a correspondence rate of:

- 63 ± 2% in the regadenoson arm (n=1,240 patients)
- 62 ± 3% in the adenosine arm (n=631 patients).

The difference in the correspondence rates (regadenoson arm – adenosine arm) was 0±3% (95% CI: [-6.2; 6.8%]; which is also a lower limit above the pre-defined threshold for the conclusion of non-inferiority).

Conclusions for efficacy

The efficacy of regadenoson is based on two phase III studies (CVT 5131 and CVT 6132).
Both of these studies, with comparable methods versus adenosine, highlighted that the correspondence rate of radionuclide myocardial perfusion images was non-inferior with regadenoson compared with adenosine.
Pooled analysis of the results is in agreement with the results from each of the individual studies.

08.2 Adverse effects

Hierarchical safety tests
In the phase III studies, the safety of regadenoson was comparable to that of adenosine. In both studies, the pre-specified endpoints to evaluate safety were tested in hierarchical order, with a significance of 5%.

For both the CVT 5131 and the CVT 5132 studies, the primary diagnostic efficacy endpoint was achieved (non-inferiority of regadenoson *versus* adenosine in terms of the correspondence rate of images). This result enabled the sequence of hierarchical tests to be carried out to compare safety.

The safety results from the two studies are presented below. The incidence and associated severity of combined "*flushing, chest pain and dyspnoea*" symptoms occurring in the 30 minutes after the administration of the stress agent was significantly lower for patients treated with regadenoson *versus* those who received adenosine (depending on the study, $p<0.001$ and $p=0.013$) (stage 1).

Table 5: Study CVT 5131 and CVT 5132 - Hierarchical safety tests – stage 1

Stage 1: Comparison of the cumulative score of "flushing, chest pain and dyspnoea" AEs			
CVT 5131		**CVT 5132**	
Regadenoson (n=820)	**Adenosine (n=411)**	**Regadenoson (n=517)**	**Adenosine (n=267)**
0.9 ± 0.03	1.3 ± 0.06	0.9 ± 0.05	1.1 ± 0.08
p<0.001		p=0.013	

For each study, the difference obtained between the two groups was statistically significant; this enabled the test to continue to stage 2.

The incidence of "*flushing*", "*chest pain", and "pain to the throat, neck and jaw"* events occurring in the 30 minutes after the administration of the stress agent was significantly lower with regadenoson *versus* adenosine (stage 2).

The incidence of the "*headache*" event occurring in the 30 minutes after the administration of the stress agent was significantly higher in the regadenoson group than that in the adenosine group (stage 2).

Table 6: Study CVT 5131 and CVT 5132 - Hierarchical safety tests – stage 2

Stage 2: Comparison of the incidence of predefined symptoms, occurring in the 30 minutes after the start of infusion.				
Symptoms	**CVT 5131**		**CVT 5132**	
	Regadenoson (n=820)	**Adenosine (n=411)**	**Regadenoson (n=517)**	**Adenosine (n=267)**
Flushing	21.7%	34.5%	20.1%	29.2%
	p<0.001		p=0.027	
Chest pain	28.5%	43.6%	26.3%	35.2%
	p<0.001		p=0.036	
Dyspnoea	29.3%	30.4%	24.8%	18.4%
	NS		NS	
Pain to the throat, neck or jaw	7.3%	13.1%	6.0%	11.6%
	p=0.006		p=0.031	
Headaches	23.3%	16.1%	27.7%	15.4%
	p=0.013		p<0.001	
Gastrointestinal discomfort	20.5%	16.1%	19.1%	10.9%
	NS		p=0.017	
Dizziness/ Vertigo	8.2%	8.0%	6.0%	3.4%
	NS		NS	

The observation of at least one value for p<0.05 during stage 2 enabled the statistical test to continue to stage 3.

Table 7: Studies CVT 5131 and CVT 5132 - Hierarchical safety tests – stage 3

Stage 3: Comparison of the percentage of patients with a reduction in SBP >25 mmHg compared with baseline.			
CVT 5131		**CVT 5132**	
Regadenoson (n=820)	**Adenosine (n=411)**	**Regadenoson (n=517)**	**Adenosine (n=267)**
17%	20%	13%	14%
NS		NS	

The proportion of patients with a reduction in systolic blood pressure (SBP) > 25 mmHg compared with baseline was not different between the two groups.
Consequently, the sequence of hierarchical tests was stopped; the results obtained subsequently for stages 4 to 7 were non-demonstrative and are therefore not presented.

General safety profile

In studies CVT 5131 and CVT 5132, 2,018 patients were randomised and received a second administration either of regadenoson or of adenosine during the randomised phase, including 3 patients (2 in the regadenoson arm and 1 in the adenosine arm) who left the study prematurely due to errors or infusion problems and for whom no safety data were reported.
Of the 2,015 patients with safety data, 1,628 (81%) patients had at least one adverse effect (AE), including: 1,063 patients (80%) in the regadenoson group and 565 patients in the adenosine arm (Table 8). The proportion of patients with treatment-related AEs or with AEs requiring treatment was comparable between the two arms (77% and 9% respectively in the regadenoson arm and 82% and 8% in the adenosine arm).
Two patients left the study prematurely in the regadenoson arm; however no patients discontinued the study in the adenosine arm.
The proportion of patients with serious adverse events (SAEs) was 1% (16/1,337) in the regadenoson group *versus* 2% (15/678) in the adenosine group.

Table 8: Studies CVT 5131 and 5132 – Summary of adverse events

	Regadenoson n= 1,337	**Adenosine n= 678**	**All n= 2,015**
Number of patients with adverse events	1,063 (80%)	565 (83%)	1,628 (81%)
Number of patients with treatment-related adverse events	1,032 (77%)	553 (82%)	1,585 (79%)
Number of patients with adverse events requiring treatment	126 (9%)	51 (8%)	177 (9%)
Number of patients discontinuing the study prematurely due to adverse events	2 (<1%)	0	2 (<1%)
Number of patients with serious adverse events	16 (1%)	15 (2%)	31 (2%)

The most commonly reported adverse events (incidence ≥5%) during treatment are presented in Table 9 according to System Organ Class (SOC) and MedDRA terminology.
The most commonly observed AEs in the regadenoson arm versus adenosine were:
- dyspnoea: 28% (369/1,337) versus 26% (173/678);
- headaches: 26% (342/1,337) versus 17% (113/678);
- rash: 16% (215/1,337) versus 25% (167/678);
- chest discomfort: 13% (168/1,337) versus 18% (119/678).

Table 9: Studies CVT 5131 and 5132: Types of adverse event (frequency ≥ 5%)

	Regadenoson n = 1,337	**Adenosine n = 678**
All patients	1,063 (80%)	565 (83%)
Nervous system disorders		
Headaches	342 (26%)	113 (17%)
Dizziness	106 (8%)	46 (7%)
Dysgueusia	71 (5%)	45 (7%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	369 (28%)	173 (26%)
Vascular disorders		
Flushing	215 (16%)	167 (25%)
General disorders and administration site conditions		
Chest discomfort	168 (13%)	119 (18%)
Chest pain	96 (7%)	69 (10%)
Feeling hot	70 (5%)	54 (8%)
Cardiac disorders		
Angina pectoris	130 (10%)	99 (15%)
Gastrointestinal disorders		
Nausea	86 (6%)	42 (6%)
Abdominal discomfort	70 (5%)	14 (2%)
Investigations		
Electrocardiogram ST segment changes	67 (5%)	45 (7%)

Death

Five deaths occurred during the two phase III studies (no other deaths had been reported during trials carried out previously), including:

- two deaths in the regadenoson arm (one death in each of the studies);
- two deaths in the adenosine arm (both in the CVT 5131 study), including one patient during the randomised phase (after having received the second administration of adenosine) and one patient in the initial open-label phase (after administration of the initial dose of adenosine);
- one death during study CVT 5131, in a patient who had received the initial dose of adenosine but had not performed the initial stress test.

None of these deaths were considered as being related to the study treatment.

Effects on heart rhythm

During studies CVT 5131 and CVT 5132, the mean increase in heart rate after administration of the dose of regadenoson or adenosine was +21 (±12) beats per minute in the regadenoson arm and +15 (±11) beats per minute in the adenosine arm.

Effects on blood pressure

Compared to baseline, both treatments were associated with a reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP). Variations were comparable for both treatments across the two parameters.

The mean variations in SBP and BPD were:

- -3 and -4 mmHg respectively in the regadenoson arm,
- -7 and -6 mmHg respectively in the adenosine arm.

Pharmacovigilance data

Since the initial marketing of the product in April 2008, four periodic pharmacovigilance reports (PSUR) are available. The cumulative exposure to regadenoson is estimated as being approximately 9,400,000 patients since it was first marketed.

The four PSURs available have led to the addition of "hypersensitivity reactions including: rash, urticaria, angioedema, anaphylaxis and/or throat tightness" and "prolonged QT interval" to the SPC (CHMP Opinion of 27 October 2011, while waiting for the decision of the European Commission).

Conclusion for safety

During both of the phase III studies, the cumulative score for the occurrence of "flushing, chest pain and dyspnoea" symptoms was lower with regadenoson compared with that observed with adenosine (1.3 ± 0.05). The incidences of "flushing" (21% versus 34% in one study and 20% versus 30% in the second), "chest pain" (28% versus 43% and 26% versus 35%) and “pain to the throat, neck or jaw" (7% versus 13% and 6% versus 12%) symptoms were reduced with regadenoson compared with adenosine.

However, the incidence of headaches (23% versus 16% and 28% versus 15%) was higher with regadenoson compared with adenosine.

The most commonly reported adverse events were dyspnoea (28%), headaches (26%), rash (16%) and chest discomfort (13%).

During the two studies, regadenoson led to a mean increase in heart rate of +21 beats per minute. Changes to blood pressure were also observed (-3 mmHg for SBP and -4 mmHg for DBP).

08.3 Summary & discussion

The efficacy of regadenoson is based on two randomised, double-blind phase III studies versus adenosine (relevant comparator) in patients for whom radionuclide myocardial perfusion imaging with a pharmacological stress agent was clinically indicated. These studies showed that the correspondence rates of radionuclide myocardial perfusion images were not inferior with pharmacological stress induced with regadenoson compared with stress induced by adenosine.

Of the adverse events reported during these two studies, "flushing", "chest pain" and "pain to the throat, neck and jaw" were less common with regadenoson than with adenosine. However, headaches were more common with regadenoson than with adenosine.

As with adenosine, regadenoson leads to a mean increase in heart rate (+21 beats per minute) and a lowering in blood pressure (-3 mmHg for SBP and -4 mmHg for DBP).

There are no studies available that have evaluated the impact of the difference in diagnostic performance provided by regadenoson compared with coronary angiography.

09 THERAPEUTIC USE

The aim of functional cardiovascular investigations is to detect potential myocardial ischaemia, which could lead to life-threatening complications for patients.
In 2009, HAS (within the scope of the assessment of non-invasive imaging in coronary disease) stated that coronary angiography, radionuclide cardiac imaging and cardiac ultrasound were the three most commonly used imaging techniques within the context of coronary disease.
Radionuclide myocardial perfusion imaging is one of the standard investigation techniques in the diagnosis and prognosis of coronary disease.[7] Coupled with SPECT, the technique enables a more accurate prognosis of the coronary disease to be given than an assessment based purely on the combination of clinical, biological, ECG and ultrasound parameters.[8]

Diagnostic and prognostic performance of radionuclide myocardial perfusion imaging remains strongly dependent on the quality of the test to induce ischaemia. The "stress" test is a standard test to induce ischaemia to carry out a radionuclide myocardial perfusion image. However, when physical exercise is contraindicated or impossible for the patient, or when physical exercise is inadequate, the physical stress test can be stimulated by the administration of a pharmacological stress agent.[9]

The most commonly used pharmacological stress agents within the context of radionuclide myocardial perfusion imaging are adenosine (ADENOSCAN) and dipyridamole (PERSANTIN), or in cases where these products are contraindicated, dobutamine.
Regadenoson is a new pharmacological stress agent to investigate coronary vascularisation during radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress.

[7] Marcassa C, Bax J J, Bengel F, Hesse B, Petersen C L et al. Clinical value, cost-effectiveness, and safety of myocardial perfusion scintigraphy: a position statement. Eur Heart J 2008; 29: 557-563.
[8] Gimelli et al. Stress/Rest Myocardial Perfusion Abnormalities by Gated SPECT: Still the Best Predictor of Cardiac Events in Stable Ischemic Heart Disease. J Nucl Med 2009; 50: 546-553.
[9] Marinque A et al. Recommendations de la SFC. Arch Mal Coeur Vaiss 2002; 95: 850-874.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above data and information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

- The seriousness of the condition is defined according to the results of the investigation. The aim of functional cardiovascular investigations is to detect potential myocardial ischaemia, which could lead to life-threatening complications for patients.
- RAPISCAN is for diagnostic use only**.**
- The efficacy/adverse effects ratio in the Marketing Authorisation indication is modest.
- Alternative diagnostic medicinal products exist (adenosine and dipyridamole).
- Like adenosine or dipyridamole, RAPISCAN is a first-line medicinal product for patients who cannot produce adequate exercise stress.

- Public health benefit:

  In the absence of data concerning the diagnostic benefit of RAPISCAN compared with other available alternatives, its impact on the health of patients requiring diagnostic investigations with the use of a pharmacological stress agent is not quantifiable.

  Given the availability of other diagnostic products, it is not expected that this medicinal product will benefit public health in its indication.

Consequently, the Committee considers that the actual benefit of RAPISCAN is low in the Marketing Authorisation indication.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

RAPISCAN, as a pharmacological stress agent for radionuclide myocardial infusion imaging in patients with coronary disease unable to undergo adequate exercise stress, does not provide an improvement in actual benefit (IAB V, non-existent).

010.3 Target population

The target population of RAPISCAN corresponds to adult patients having radionuclide myocardial perfusion imaging and unable to undergo adequate exercise stress.
In France, 220,000[10] to 254,000[11] radionuclide myocardial perfusion imaging investigations are performed per year. Between 46%[10] and 57%[11] of these radionuclide investigations are carried out with the injection of a pharmacological stress agent.
On this basis, the target population of RAPISCAN would be between **101,200** and **144,780** patients.

[10] Beaulieu JL, Moundler O. Activité des services de medicine nucléaire face aux grands enjeux de santé publique en France. Médecine nucléaire 2008; 38: 620-622.
[11] Reyes E, Wiener S, Underwood SR; European Council of Nuclear Cardiology. Myocardial perfusion scintigraphy in Europe 2007: a survey of the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging 2012; 39: 160-164.