

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215168Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLYRCADO™ safely and effectively. See full prescribing information for FLYRCADO.

FLYRCADO™ (flurpiridaz F 18) injection, for intravenous use
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

FLYRCADO is a radioactive diagnostic drug indicated for positron emission tomography (PET) myocardial perfusion imaging (MPI) under rest or stress (pharmacologic or exercise) in adult patients with known or suspected coronary artery disease (CAD) to evaluate for myocardial ischemia and infarction. (1)

DOSAGE AND ADMINISTRATION

- Administer FLYRCADO via intravenous injection. (2.2)
- When rest and stress imaging are conducted on the same day, the recommended administered activities are (2.2):
 - Rest imaging: 93 MBq to 111 MBq (2.5 mCi to 3 mCi)
 - Pharmacologic stress imaging: 222 MBq to 241 MBq (6 mCi to 6.5 mCi)
 - Exercise stress imaging: 333 MBq to 352 MBq (9 mCi to 9.5 mCi)
- When rest and stress imaging are conducted over two days, the recommended rest and stress administered activities, for both pharmacologic and exercise stress, are 93 MBq to 111 MBq (2.5 mCi to 3 mCi). (2.2)
- See full prescribing information for radiation safety, preparation, administration, imaging, and radiation dosimetry information. (2.1, 2.2, 2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 190 MBq/mL to 2,050 MBq/mL (5 mCi/mL to 55 mCi/mL) of flurpiridaz F 18 at end of synthesis in a shielded multiple-dose vial with up to 30 mL fill volume (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Risk associated with exercise or pharmacologic stress: Serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, broncho-constriction, stroke, and seizures may occur. Perform stress testing in the setting where cardiac resuscitation equipment and trained staff are readily available. When pharmacologic stress is selected, perform the procedure in accordance with the pharmacologic stress agent’s prescribing information. (5.1)
- Radiation risks: Ensure safe handling to minimize radiation exposure to patients and health care providers. (5.2)

ADVERSE REACTIONS

Most common adverse reactions occurring during FLYRCADO PET MPI under rest and stress (pharmacologic or exercise) (incidence ≥ 2%) are dyspnea, headache, angina pectoris, chest pain, fatigue, ST segment changes, flushing, nausea, abdominal pain, dizziness, and arrhythmia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GE HealthCare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Lactation: Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for at least 8 hours after FLYRCADO administration. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Radiation Safety – Drug Handling
 - 2.2 Recommended Dosage, Preparation, and Administration Instructions
 - 2.3 Image Acquisition Instructions
 - 2.4 Radiation Dosimetry
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
 - 5.1 Risks Associated with Exercise or Pharmacologic Stress
 - 5.2 Radiation Risks
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use

- 11 DESCRIPTION
 - 11.1 Chemical Characteristics
 - 11.2 Physical Characteristics
 - 11.3 External Radiation
- 12 CLINICAL PHARMACOLOGY
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
 - 14.1 Overview of Clinical Studies
 - 14.2 Suspected Coronary Artery Disease
 - 14.3 Known or Suspected Coronary Artery Disease
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLYRCADO is indicated for positron emission tomography (PET) myocardial perfusion imaging (MPI) under rest or stress (pharmacologic or exercise) in adult patients with known or suspected coronary artery disease (CAD) to evaluate for myocardial ischemia and infarction.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety – Drug Handling

Handle FLYRCADO with appropriate safety measures to minimize radiation exposure [see *Warnings and Precautions* (5.2)]. Use waterproof gloves and effective shielding, including lead-glass syringe shields, when handling and administering FLYRCADO.

Radioactive drugs should be used by or under the control of healthcare providers who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

2.2 Recommended Dosage, Preparation, and Administration Instructions

Recommended Dosage

- The recommended activity for each type of examination is presented in [Table 1](#).
- Administer two doses by intravenous injection, one for rest imaging and one for stress imaging, using either pharmacologic or exercise stress, in either a 1-day or 2-day protocol.
- If performing a combined exercise/pharmacologic stress protocol, administer the recommended activity for pharmacologic stress.
- When rest and stress imaging are performed on the same day, the recommended minimum stress activity is 2-fold the rest activity for pharmacologic stress and 3-fold the rest activity for exercise stress to provide adequate image quality and obscure residual signal from the first acquisition.
- The recommended maximum total volume administered in one day is 6.1 mL.

Table 1 – Recommended Administered Activities of FLYRCADO in Adults for Rest and Stress Imaging Using Pharmacologic or Exercise Stress in a 1-Day or 2-Day Protocol

Length of Protocol	Activity for Rest Imaging	Activity for Stress Imaging	
		Pharmacologic	Exercise
1 day	93 MBq to 111 MBq (2.5 mCi to 3 mCi)	222 MBq to 241 MBq (6 mCi to 6.5 mCi)	333 MBq to 352 MBq (9 mCi to 9.5 mCi)
2 days	93 MBq to 111 MBq (2.5 mCi to 3 mCi)	93 MBq to 111 MBq (2.5 mCi to 3 mCi)	93 MBq to 111 MBq (2.5 mCi to 3 mCi)

Patient Preparation

Instruct patients to drink water to ensure adequate hydration prior to administration of FLYRCADO and to continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure [see *Warnings and Precautions* (5.2)].

Drug Preparation

- Use aseptic technique and radiation shielding to withdraw and administer FLYRCADO.
- Calculate the necessary volume to administer based on calibration time and activity using a suitably calibrated instrument.

- Visually inspect FLYRCADO for particulate matter and discoloration prior to administration and do not use if either is observed.
- Ensure the correct syringe is used and has adequate volume (at least 1 mL to 2 mL) so that the activity in the syringe can be administered without excessive dead volume loss.
- Measure patient dose using a dose calibrator immediately before administration.
- Do not use and discard FLYRCADO 8 hours after end of synthesis or when the activity falls below the activity requirement at the time of injection, whichever is earlier.
- FLYRCADO may be diluted aseptically with 0.9% Sodium Chloride Injection, USP. Diluted product should be used within 8 hours after end of synthesis or when the activity falls below the activity requirement at the time of injection, whichever is earlier.
- Dispose of unused product in a safe manner and in compliance with applicable regulations.

Administration Instructions

- Administer FLYRCADO via intravenous injection as a bolus lasting less than 10 seconds and immediately follow with a flush of 0.9% Sodium Chloride Injection, USP.
- The minimum time between rest and stress dose administration is:
 - 30 minutes when using pharmacologic stress
 - 60 minutes when using exercise stress
- When using pharmacologic stress, administer FLYRCADO at the time of peak vasodilation according to the prescribing information for the stress agent, using an intravenous port different from the one used for the stress agent.
- When using exercise stress, administer FLYRCADO after the patient reaches at least 85% of their age-predicted maximum heart rate or exhibits ischemic signs or symptoms. The patient should then continue to exercise for approximately 1 minute to 2 minutes after the injection. If the patient cannot achieve the target heart rate, the examination may be converted to pharmacologic stress.

2.3 Image Acquisition Instructions

For rest and stress imaging, image reconstruction should include attenuation correction.

Rest Imaging

Begin the PET acquisition 5 minutes after FLYRCADO administration and acquire images for 10 minutes using a scanner in 3D mode.

Pharmacologic Stress Imaging

Begin the PET acquisition 5 minutes after FLYRCADO administration and acquire images for 10 minutes using a scanner in 3D mode.

Optionally, dynamic imaging may be performed, starting immediately prior to the injection of FLYRCADO.

Exercise Stress Imaging

Once the patient has been positioned on the scanner and respiration has begun to return to normal, begin image acquisition (about 15 minutes to 25 minutes after administration of FLYRCADO). Acquire images for 10 minutes using a scanner in 3D mode.

2.4 Radiation Dosimetry

[Table 2](#) shows the estimated radiation absorbed doses per unit of injected activity.

Table 2 – Estimated Radiation Absorbed Doses in Organs/Tissues from Intravenous Administration of FLYRCADO in Adults

Organ	Absorbed Dose per Unit of Administered Activity (mGy/MBq)		
	Rest	Pharmacologic Stress*	Exercise Stress
Adrenals	0.016	0.016	0.014
Bone surfaces	0.019	0.019	0.02
Brain	0.025	0.022	0.011
Breasts	0.009	0.009	0.01
Gallbladder Wall	0.017	0.018	0.015
Gastrointestinal Tract			
Stomach Wall	0.04	0.033	0.024
Small Intestine Wall	0.013	0.012	0.014
Upper Large Intestine Wall	0.013	0.012	0.014
Lower Large Intestine Wall	0.012	0.011	0.014
Heart Wall	0.048	0.09	0.039
Kidneys	0.066	0.057	0.027
Liver	0.039	0.044	0.015
Lungs	0.011	0.012	0.012
Muscle	0.01	0.01	0.012
Ovaries	0.012	0.012	0.014
Pancreas	0.016	0.016	0.015
Red Marrow	0.016	0.018	0.015
Salivary Glands	0.035	0.076	0.007
Skin	0.008	0.008	0.009
Spleen	0.016	0.012	0.013
Testes	0.009	0.009	0.011
Thymus	0.011	0.012	0.013
Thyroid	0.032	0.036	0.014
Urinary Bladder Wall	0.023	0.021	0.016
Uterus	0.012	0.012	0.014
Total Body	0.012	0.012	0.012
Effective Dose (mSv/MBq)	0.019	0.019	0.015

*The pharmacologic stress agent used was adenosine.

The whole-body effective dose resulting from the administration of maximal activity of FLYRCADO of 111 MBq at rest, 241 MBq during pharmacological stress, and 352 MBq during exercise stress is, respectively, 2.1 mSv, 4.6 mSv, and 5.3 mSv. Under the same conditions, the absorbed dose to the target organ (heart wall) is 5.3 mGy, 22 mGy, and 14 mGy for each administered activity, respectively.

The use of a CT scan to calculate attenuation correction for the reconstruction of FLYRCADO PET images (as done in PET/CT imaging) will add radiation exposure.

3 DOSAGE FORMS AND STRENGTHS

Injection: 190 MBq/mL to 2,050 MBq/mL (5 mCi/mL to 55 mCi/mL) of flurpiridaz F 18 at end of synthesis as a clear, colorless to yellow solution in a shielded multiple-dose vial with up to 30 mL fill volume.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risks Associated with Exercise or Pharmacologic Stress

Patients evaluated with exercise or pharmacologic stress may experience serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, stroke, and seizure. Perform stress testing in the setting where cardiac resuscitation equipment and trained staff are readily available. When pharmacologic stress is selected as an alternative to exercise, perform the procedure in accordance with the pharmacologic stress agent's prescribing information.

5.2 Radiation Risks

FLYRCADO contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk of cancer. Ensure safe handling to minimize radiation exposure to patients and health care providers [see *Dosage and Administration* (2.1, 2.4)]. Advise patients to hydrate before and after administration and to void frequently after administration.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Risks Associated with Exercise or Pharmacologic Stress [see *Warnings and Precautions* (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of FLYRCADO was evaluated in 1,600 subjects in clinical studies, including 1,575 (98%) subjects with known or suspected coronary artery disease and 25 (2%) healthy subjects. All 1,600 subjects were dosed under rest conditions, with a mean dose of 102 MBq (2.8 mCi) FLYRCADO. A total of 1,568 (98%) subjects were also dosed under stress (exercise or pharmacologic) conditions, with a mean activity of 252 MBq (6.8 mCi) FLYRCADO by intravenous route. The demographic characteristics of the study population were 31% female, mean age 62 years (range 19 years to 90 years), 81% White, 11% Black or African American, 1% Asian, and 7% other or unreported race, and 10% Hispanic or Latino, 81% Not Hispanic or Latino, and 9% unreported ethnicity.

Stress testing procedures are associated with serious adverse reactions [see *Warnings and Precautions* (5.1)]. Adverse reactions occurring in ≥2% subjects receiving FLYRCADO during PET MPI under rest and stress (pharmacologic or exercise) are presented in Table 3.

Table 3. Adverse Reactions Reported in $\geq 2\%$ of Subjects During FLYRCADO PET MPI Under Rest and Stress (Pharmacologic or Exercise)

Adverse Reaction	FLYRCADO PET MPI Under Rest and Stress (Pharmacologic or Exercise) N=1,600* %
Dyspnea	17
Headache	15
Angina pectoris	10
Chest pain	8
Fatigue	7
ST segment changes	6
Flushing	5
Nausea	4
Abdominal pain	4
Dizziness	4
Arrhythmia	4

*Includes 32 subjects who received only one dose at rest.

Adverse reactions occurring during FLYRCADO PET MPI under rest and stress (pharmacologic or exercise) in $< 2\%$ of subjects included diarrhea, palpitations, back pain, cardiac conduction disturbance, rash, dysgeusia, cough, hypotension, anxiety, vomiting, pruritus, bronchospasm, dry mouth, blood pressure elevation, syncope, and wheezing.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on use of flurpiridaz F 18 in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

All radiopharmaceuticals, including FLYRCADO, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering FLYRCADO administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from flurpiridaz F 18 and the gestational timing of exposure.

FLYRCADO contains ethanol (a maximum daily dose of 337 mg anhydrous ethanol). The lower limit of safety for ethanol use during pregnancy has not been established. Published studies have demonstrated that ethanol is associated with fetal harm including central nervous system abnormalities, behavioral disorders, and impaired intellectual development. If considering FLYRCADO administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes associated with ethanol exposure during pregnancy.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of flurpiridaz F 18 or its metabolites in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. Based on clinical guidelines, exposure of FLYRCADO to a breastfed infant can be minimized by advising a lactating woman to temporarily discontinue breastfeeding and to pump and discard breast milk for a minimum of 8 hours after administration of FLYRCADO. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FLYRCADO and any potential adverse effects on the breastfed child from FLYRCADO or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of FLYRCADO in pediatric patients have not been established.

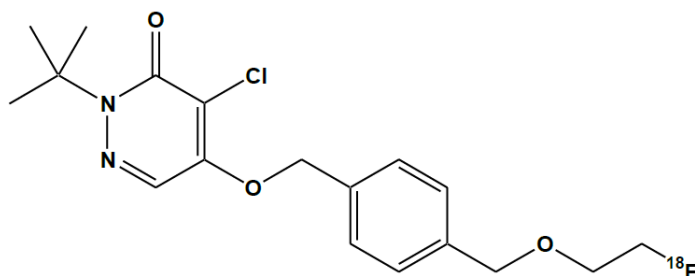
8.5 Geriatric Use

Of 1,600 subjects in clinical studies of FLYRCADO, 720 (45%) were 65 years of age and over and 181 (11%) were 75 years of age or older. No overall differences in safety or effectiveness of FLYRCADO have been observed between patients 65 years of age and older and younger adult patients.

11 DESCRIPTION

11.1 Chemical Characteristics

FLYRCADO (flurpiridaz F 18) injection is a radioactive diagnostic drug for intravenous use. The molecular formula of flurpiridaz F 18 is $C_{18}H_{22}Cl^{18}FN_2O_3$, the molecular mass is 367.8, and the structural formula is:



Chemically, flurpiridaz F 18 is 2-*tert*-butyl-4-chloro-5-[[4-(2-(^{18}F)fluoranylethoxymethyl)phenyl]methoxy]pyridazin-3-one.

FLYRCADO is a sterile, preservative-free, non-pyrogenic, clear, colorless to yellow radioactive solution. Each mL contains 190 MBq to 2,050 MBq (5 mCi to 55 mCi) of flurpiridaz F 18 at end of synthesis, up to 2.3 mcg flurpiridaz, and the following inactive ingredients: 45 mg hydroxypropyl- β -cyclodextrin (as a solubilizer and co-radiostabilizer), 35 mg L-(+)-ascorbic acid (as a radiostabilizer), 8.2 mg sodium hydroxide, and 55.2 mg anhydrous ethanol, in water for injection. The pH of the solution is between 5.5 and 8.

11.2 Physical Characteristics

Fluorine-18 decays by positron (β^+) emission and has a half-life of 109.8 minutes. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron. Principal emission data for fluorine-18 are shown in [Table 4](#).

Table 4 – Principal Radiation Emission Data for Fluorine-18

Radiation/Emission	% per Disintegration	Mean Energy (keV)
Positron	96.7	249.8
Gamma	193.5	511

11.3 External Radiation

The point source air-kerma rate constant for fluorine-18 is $3.74\text{E-}17 \text{ Gy m}^2/(\text{Bq s})$; this coefficient was formerly defined as the specific gamma-ray constant of 5.7 R/hr/mCi at 1 cm. The first half-value thickness of lead (Pb) for fluorine-18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by fluorine-18 that results from various thicknesses of lead shielding is shown in [Table 5](#). The use of about 8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.

Table 5 - Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shielding Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Flurpiridaz F 18 is an analog of the mitochondrial complex 1 (MC-1) inhibitor, pyridaben. Flurpiridaz F 18 is extracted by the myocardium proportional to the blood flow and binds to heart tissue that has biologically active mitochondria. Therefore, radioactivity in viable myocardium is higher than in infarcted tissue.

12.2 Pharmacodynamics

The relationship between flurpiridaz F 18 plasma concentrations and successful imaging was not explored in clinical trials.

12.3 Pharmacokinetics

The pharmacokinetics of flurpiridaz F 18 were evaluated in healthy subjects. Blood radioactivity peaked at 2.3 minutes with blood clearance followed by a rise and plateau at around 3% of the 296 MBq (8 mCi) flurpiridaz F 18 intravenous dose until 7 hours post administration. The fluorine-18 radioactivity in blood during the first 15-minutes post administration was associated with flurpiridaz while it was associated with flurpiridaz metabolites thereafter.

Distribution

Flurpiridaz F 18 distributes to the liver (19% of injected activity), kidneys (9%), brain (8%), and heart wall (3%) about 10 minutes post-dose. The heart wall radioactivity was retained for 1 hour after administration.

Elimination

Flurpiridaz F 18 and its metabolites were cleared from blood within 48 hours.

Metabolism

Flurpiridaz F 18 was shown to undergo biotransformation to numerous polar metabolites.

Excretion

Following intravenous administration of a single dose of ³H-radiolabeled flurpiridaz, 63% of the administered dose was recovered in urine (0% unchanged flurpiridaz) and 30% in feces (0% unchanged flurpiridaz).

Specific Populations

No clinically significant differences in the pharmacokinetics of flurpiridaz F 18 were observed for age, sex, body mass index, diabetic status, mild hepatic impairment (Child Pugh A), or renal impairment (eGFR ≥19 to 89 mL/min). The effect of moderate to severe hepatic impairment (Child Pugh B and C) or end stage renal disease on flurpiridaz F 18 pharmacokinetics has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenicity studies of flurpiridaz have been conducted.

Mutagenesis

Flurpiridaz did not demonstrate mutagenic potential in an in vitro bacterial reverse mutation assay (Ames test), in an in vitro chromosome aberration assay in Chinese hamster ovary cells, or in an in vivo rat micronucleus assay.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

The safety and effectiveness of FLYRCADO were evaluated in two prospective, multicenter, open-label clinical studies in adults with either suspected coronary artery disease (CAD) (Study 1: NCT03354273) or known or suspected CAD (Study 2: NCT01347710).

Subjects received two injections of FLYRCADO: one at rest and one during stress [see *Dosage and Administration* (2.2, 2.3)]. For the FLYRCADO stress injection, subjects received either a pharmacologic stress agent or engaged in exercise stress. PET myocardial perfusion imaging (MPI) was performed at both rest and stress using cardiac gating and low-dose CT attenuation correction. Subjects also received rest and stress SPECT MPI using technetium Tc 99m sestamibi or technetium Tc 99m tetrofosmin on a different day from the PET MPI. The stress modality was to be the same for PET and SPECT.

Stress and rest images were displayed side-by-side for the assessment of perfusion and wall motion abnormalities. Three qualified readers, blinded to clinical data, performed independent assessment of each subject's rest and stress images, with each recording an overall qualitative diagnosis of normal, ischemia, ischemia plus scar, or scar. For analyses of sensitivity and specificity, normal was considered image negative and all other diagnoses were considered image positive.

14.2 Suspected Coronary Artery Disease

Study 1 evaluated the sensitivity and specificity of FLYRCADO PET MPI for the detection of significant CAD in subjects with suspected CAD who were scheduled for invasive coronary angiography (ICA).

A total of 578 subjects were evaluable for effectiveness, having rest and stress imaging and evaluable truth standard data. Subjects ranged in age from 26 years to 88 years, with a mean age of 64 years. A total of 188 (33%) were female, and 473 (82%) were White, 35 (6%) were Black or African American, 6 (1%) were Asian, and 64 (11%) were other races or not reported. In addition, 79 subjects (14%) reported Hispanic/Latino ethnicity. Pharmacologic stress was performed in 83% of subjects and exercise stress in 17% of subjects.

The sensitivity and specificity of FLYRCADO PET MPI for detection of significant CAD, defined as the presence of significant stenosis in at least one major epicardial coronary artery or major branch by quantitative coronary angiography (QCA) are reported in Table 6. Results for both $\geq 50\%$ stenosis and a secondary analysis using $\geq 70\%$ stenosis as the threshold for significant CAD are shown.

Table 6. Diagnostic Performance of FLYRCADO PET MPI in Study 1 (N = 578*)

Reader	$\geq 50\%$ Stenosis Reference Standard		$\geq 70\%$ Stenosis Reference Standard	
	Sensitivity (95% CI) N=249	Specificity (95% CI) N=329	Sensitivity (95% CI) N=127	Specificity (95% CI) N=449
Reader 1	77% (72%, 82%)	66% (61%, 71%)	91% (86%, 96%)	58% (54%, 63%)
Reader 2	74% (68%, 79%)	70% (65%, 75%)	87% (82%, 93%)	62% (58%, 67%)
Reader 3	89% (85%, 93%)	53% (47%, 58%)	97% (94%, 100%)	44% (39%, 49%)

Abbreviations: CI = confidence interval, MPI = myocardial perfusion imaging

*Includes 12 subjects who had reference standard images categorized as uninterpretable by the central reader but were forced to be diagnosed as positive or negative (2 subjects as positive and 10 subjects as negative).

From a blinded re-evaluation of 60 randomly selected PET MPI images presented during the main reading sessions, intra-reader kappa ranged from 0.71 to 0.93 for the three readers.

Using a 50% stenosis threshold, sensitivity of SPECT MPI was 61% to 76% for the three readers, with the lower bound of the 95% confidence intervals ranging from 55% to 70%, and specificity of SPECT MPI was 51% to 65%, with the lower bound of the 95% confidence intervals ranging from 46% to 60%.

14.3 Known or Suspected Coronary Artery Disease

Study 2 evaluated the sensitivity and specificity of FLYRCADO PET MPI for the detection of significant CAD in subjects with known or suspected CAD who had ICA without intervention within 60 days prior to imaging or were scheduled for ICA.

A total of 755 subjects were evaluable for effectiveness, having rest and stress imaging for FLYRCADO PET and evaluable truth standard data. Subjects ranged in age from 36 years to 90 years, with a mean age of 63 years. A total of 235 (31%) were female, and 619 (82%) were White, 101 (13%) were Black or African American, 8 (1%) were Asian, and 24 (4%) were other races or not reported. Pharmacologic stress was performed in 71% of subjects and exercise stress in 29% of subjects.

The sensitivity and specificity of FLYRCADO PET MPI for the detection of significant CAD, defined as the presence of significant stenosis in at least one major epicardial coronary artery or major branch by QCA or as history of myocardial infarction are reported in Table 7. Results for both $\geq 50\%$ stenosis and a secondary analysis using a threshold of $\geq 70\%$ stenosis for significant CAD are shown.

Table 7. Diagnostic Performance of FLYRCADO PET MPI in Study 2 (N = 755)

Reader	$\geq 50\%$ Stenosis or Confirmed MI Reference Standard		$\geq 70\%$ Stenosis or Confirmed MI Reference Standard	
	Sensitivity (95% CI) N=352	Specificity (95% CI) N=403	Sensitivity (95% CI) N=245	Specificity (95% CI) N=510
Reader 1	73% (68%, 78%)	73% (68%, 77%)	82% (77%, 87%)	68% (63%, 71%)
Reader 2	63% (57%, 67%)	86% (82%, 89%)	72% (66%, 78%)	80% (77%, 83%)
Reader 3	77% (72%, 80%)	66% (62%, 71%)	85% (80%, 89%)	61% (57%, 66%)

Abbreviations: CI = confidence interval, MI = myocardial infarction, MPI = myocardial perfusion imaging

From a blinded re-evaluation of a randomly selected 10% of PET MPI images presented during the main reading sessions, intra-reader agreement ranged from 90% to 95% for the three readers.

Using a 50% stenosis threshold, sensitivity of SPECT MPI was 43% to 58% for the three readers, with the lower bound of the 95% confidence intervals ranging from 38% to 53%, and specificity for SPECT MPI was 80% to 92%, with the lower bound of the 95% confidence intervals ranging from 76% to 89%.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

FLYRCADO (flurpiridaz F 18) injection is a clear, colorless to yellow solution containing 190 MBq/mL to 2,050 MBq/mL (5 mCi/mL to 55 mCi/mL) of flurpiridaz F 18 at end of synthesis, supplied in a shielded multiple-dose vial (NDC 0407-8787-01) with up to 30 mL fill volume.

Storage and Handling

Store FLYRCADO at 2°C to 30°C (36°F to 86°F); excursions to -20°C (-4°F) (up to 2 hours) or to 50°C (122°F) (up to 8 hours) may be permitted. Store FLYRCADO within radiation shielding. The product does not contain a preservative.

Do not use and discard FLYRCADO 8 hours after end of synthesis or when the activity falls below the radioactivity requirement at the time of injection, whichever is earlier. The expiration date and time are provided on the shield label.

Dispose of the product in accordance with all federal, state, and local laws and institutional requirements.

This preparation is for use by persons licensed by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

17 PATIENT COUNSELING INFORMATION

Adequate Hydration

Instruct patients to drink water to ensure adequate hydration prior to administration of FLYRCADO and to continue drinking and voiding frequently during the first hours following administration to reduce radiation exposure [see *Warnings and Precautions* (5.2)].

Pregnancy

Inform pregnant women of the risks of fetal exposure to radiation dose if they undergo a radionuclide procedure and the potential risk of exposure to ethanol which is present in FLYRCADO [see *Use in Specific Populations* (8.1)].

Lactation

Advise a lactating woman to temporarily discontinue breastfeeding and to pump and discard breast milk for at least 8 hours after FLYRCADO administration to minimize radiation exposure to a breastfed infant [see *Use in Specific Populations* (8.2)].

Distributed by
GE Healthcare Inc.
Marlborough, MA 01752
USA

FLYRCADO™ is a trademark of GE HealthCare.

GE is a trademark of General Electric Company used under trademark license.

© 2024 GE HealthCare

Flyrcado (flurpiridaz F 18) injection

30 mL Vial Label

NDC 0407-8767-01		Flyrcado™		 CAUTION RADIOACTIVE MATERIAL
Multiple-Dose Vial		(flurpiridaz F 18) injection		
Non-Pyrogenic		190 MBq/mL to 2,050 MBq/mL		
Sterile		(5 mCi/mL to 55 mCi/mL) at end of synthesis		
Diagnostic - For Intravenous Use Only				
Total: _____ MBq (_____ mCi) in _____ mL at _____ on date _____				
Concentration: _____ MBq/mL (_____ mCi/mL) Exp Date _____ Exp Time _____				
Batch No.: _____ Date: _____ Vial No.: _____				
Store FLYRCADO at 2°C to 30°C (36°F to 86°F); excursions to -20°C (-4°F) (up to 2 hours) or to 50°C (122°F) (up to 8 hours) may be permitted.				
Recommended Dosage: See Prescribing Information				
Distributed by GE Healthcare Inc., Marlborough, MA 01752, U.S.A.				
				Rx ONLY 200112-0A

Flyrcado (flurpiridaz F 18) injection

30 mL Shield Label

NDC 0407-8787-01 Non-Pyrogenic Sterile	Flyrcado™ (flurpiridaz F 18) injection Multiple-Dose Vial 190 MBq/mL to 2,050 MBq/mL (5 mCi/mL to 55 mCi/mL) at end of synthesis Diagnostic - For Intravenous Use Only	
Total _____ MBq (____ mCi) in _____ mL at _____:_____ on date _____ Batch No.: _____ Exp. Date: _____ Exp. Time: _____:_____ Concentration: _____ MBq/mL (____ mCi/mL) Vial No.: _____ Each mL contains up to 2.3 mcg flurpiridaz, 45 mg hydroxypropyl-β-cyclodextrin, 35 mg L-(+)-ascorbic acid, 8.2 mg sodium hydroxide, and 55.2 mg anhydrous ethanol in water for injection. Store Flyrcado at 2°C to 30°C (36°F to 86°F); excursions to -20°C (-4°F) (up to 2 hours) or to 50°C (122°F) (up to 8 hours) may be permitted. Recommended Dosage: See Prescribing Information Rx ONLY Distributed by GE Healthcare Inc., Marlborough, MA 01752 U.S.A. 200113-0A		

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THUY M NGUYEN
09/27/2024 01:45:00 PM

ALEXANDER GOROVETS
09/27/2024 01:51:13 PM