CLINICAL REVIEW

Application Type	NDA 19-785
Submission Number	018
Submission Code	PM
Letter Date	10/29/07
Stamp Date	10/29/07
PDUFA Goal Date	04/30/08
Reviewer Name	Robert J. Yaes, MD
Review Completion Date	04/03/08
Established Name	Tc 99m Sestamibi
Trade Name	Cardiolite
Pharmacologic Class	Diagnostic Radiopharmaceutical
Applicant	Bristol Myers Squibb
Priority Designation	P
Formulation	IV
Indication	Myocardial Imaging
Intended Population	Patients with Kawasaki Disease

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1 Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

Efficacy supplement for myocardial perfusion images imaging pediatric patients with Kawasaki's Disease should not be approved

A labeling supplement for incorporation of pediatric safety data from studies of pediatric patients with Kawasaki's Disease should be approved. Additional negotiations with the sponsor, regarding the wording of the revised label is required

Risk Benefit Assessment

Principal risks associated with Cardiolite rest/stress myocardial perfusion imaging are:

Small lifetime risk of radiation induced cancer from diagnostic dose of radiation
Risk associated with exercise induced stress in patients who may have an underlying cardiac condition

Because of the low sensitivity of Cardiolite myocardial perfusion imaging with either coronary angiography or cardiac events at 6 months as a standard of truth, no clear benefit of Cardiolite myocardial perfusion imaging in pediatric patients with Kawasaki's disease has been demonstrated

Recommendations for Postmarketing Risk Management Activities

No additional post marketing risk management activity is indicated at this time

Recommendations for other Post Marketing Study Commitments

For study DuP 843-302 the sponsor has made a post marketing commitment to contact patients 10 years after imaging to obtain 10 year cardiac event data

2 Introduction and Regulatory Background

Product Information

Cardiolite (^{99m}Tc Sestamibi) is a diagnostic radiopharmaceutical agent used for myocardial perfusion imaging

Tables of Currently Available Treatments for Proposed Indications

Pediatric patients with Kawasaki disease are currently monitored for cardiac complications with coronary angiography and/or cardiac ultrasound

Availability of Proposed Active Ingredient in the United States

Cardiolite used in Kawasaki disease patients is identical to the product with the same name that is currently marketed in the US for myocardial perfusion imaging of patients with atherosclerotic coronary artery disease. Active ingredients are currently available in the United States

Important Safety Issues With Consideration to Related Drugs

Very small increase in lifetime cancer risk due to exposure to low dose ionizing radiation

Induction of cardiovascular stress has been associated with serious adverse events including myocardial infarction, arrhythmia, bronchial constriction, cerebrovascular events and death.

Rare association with allergic and anaphylactic events

Summary of Pre-submission Regulatory Activity Related to Submission

12/1990 Cardiolite (^{99m}Tc Sestamibi) is approved for myocardial perfusion imaging in adults [redacted]

6/21/2004 Proposed Pediatric Study Request for pediatric patients with Kawasaki disease submitted.

8/21/2004 Pediatric Study Request for pediatric patients with Kawasaki disease is granted. Pediatric study request includes requests for three studies in pediatric patients with Kawasaki disease:

1) A dosimetry/pharmacokinetics study of Cardiolite in pediatric subjects
2) A prospective safety and efficacy study of Cardiolite in pediatric patients with Kawasaki disease
3) A retrospective (case history) study of safety and efficacy in pediatric patients with Kawasaki disease who have been imaged with Cardiolite in the last 10 years

1/16/2007 Type C meeting with sponsor

10/29/2007 Reports of pediatric studies in PSR /Labeling supplement submitted

1/9/2008 Pediatric Exclusivity Board meeting: Pediatric exclusivity granted

Other Relevant Background Information

Cardiolite has been used for myocardial imaging in adults since 1990

3 Ethics and Good Clinical Practices

Submission Quality and Integrity

There were no pre-clinical study reports included in this submission

Reports of three International multi-center clinical studies were submitted

Each of these studies was conducted in accord with all with all country and local requirements regarding ethical committee review and informed consent. In both prospective clinical studies (201 and 301), informed consent was obtained from each parent or guardian before any study related procedures were performed. All subjects enrolled in these studies were scheduled to receive Cardiolite scans as part of their medical management. No subject received any radiopharmaceutical drug solely for the purpose of this study

Compliance with Good Clinical Practices

Bristol Myers Squibb Medical Imaging Inc. (BMS MI) monitored the clinical studies and was also responsible for all clinical supplies

Financial Disclosures

Financial disclosure form OMB-0910-0396 covering all submitted studies has been signed by Qi Zhu MD, Clinical director Bristol Myers Squibb Medical Imaging is included in this submission

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Chemistry Manufacturing and Controls

This product is identical to the approved product currently marketed for the imaging of atherosclerotic coronary artery disease in adults (See CMC section of NDA-19,785)

Clinical Microbiology

This product is identical to the approved product currently marketed for the imaging of atherosclerotic coronary artery disease in adults (See Microbiology section of NDA-19,785)Preclinical Pharmacology/Toxicology

This product is identical to the approved product currently marketed for the imaging of atherosclerotic coronary artery disease in adults. There were no preclinical studies performed on immature animals for this pediatric efficacy supplement (See Pharm/Tox section of NDA-19,785)

Clinical Pharmacology

Mechanism of Action

^{99m}Tc Sestamibi has been found to accumulate in viable myocardial tissue in a manner similar to that of thallous chloride. In preclinical studies, electron microscopy and analysis of sub-cellular fractions of heart cell aggregates suggest that Cardiolite uptake in myocardial cells occurs principally in the mitochondria Myocardial uptake is coronary artery flow dependent and can be used as an indicator of myocardial perfusion.

Pharmacodynamics

^{99m}Tc Sestamibi has been found to accumulate in viable myocardial tissue. Myocardial uptake is coronary artery flow dependent. In adult patients with documented myocardial

infarction, imaging revealed the infarct up to four hours post dose % ID in the heart is 1.5-2% at 15 minutes decreasing to 1.2% at 4 hours. % ID in the liver is 26% at 15 minutes decreasing to 9% at 90 minutes

Pharmacokinetics

In adults, the agent is eliminated without evidence of metabolism. The major path of elimination is through the hepatobilliary system. Activity from the gallbladder appears in the intestines within one hour of dosing. 33% of the injected dose is cleared through the feces and 27% is excreted in the urine. Blood clearance occurs with an initial half life of 4.3 minutes at rest and 1.6 minutes under exercise stress .Biological half life in the liver is 30 min and approximately 6 hours in the heart. The physical half-life of ^{99m}Tc is 6.02 hours.

Pediatric Pharmacokinetics, biodistribution and dosimetry has been studied in a Phase 1-2 open label non-randomized multicenter study to determine the dosimetry, pharmacokinetics (PK) and safety of Cardiolite in pediatric subjects who were scheduled to undergo a rest or stress Cardiolite single photon emission computed tomography (SPECT) imaging study. Age groups studied included both children and adolescents.78 subjects were imaged including 39 children 4 years to < 12 years and 39 adolescents ≥12 years to < 17 years. 27 subjects were evaluated at rest and 51 were evaluated under induced cardiac stress. There were 35 Asian, 31 white, 6 Black, 2 Native American, 4 other. PK parameters obtained were Blood AUC as % of injected dose, terminal phase elimination half life and mean residence time in specific source organs. Using OLINDA software, mean radiation absorbed doses were obtained for the standard set of target organs using Christy-Eckerman pediatric phantoms

Organs that received the highest doses were as follows:
Upper large intestine.....0.30 rad/mCi
Small intestine.....0.16 rad/mCi
Gall bladder.....0.16 rad/mCi
Lower large intestine.....0.13 rad/mCi

These results are consistent with elimination by the liver in the bile through the intestines as the principal route of elimination from the body

(See PK review)

5 Sources of Clinical Data

Tables of Clinical Studies

Study 1 (Protocol DuP 843-201): Pediatric Radiation Dosimetry Determination and Pharmacokinetic (Biodistribution) Study

Study 2 (Protocol DuP 843-301): Pediatric Diagnostic Efficacy and Safety Study (Prospective Study)

Study 3 (Protocol DuP 843-302): Pediatric Diagnostic Efficacy and Safety Study (Retrospective Study)

Review Strategy

The safety and efficacy data in the three pediatric studies in this submission have been reviewed. Safety was evaluated in studies DuP 843-201, DuP 843-301 and DuP 843-302. Efficacy was evaluated in studies DuP 843-301 and DuP 843-302.

Discussion of Individual Studies

Study 1 (Protocol DuP 843-201):

A Phase 1-2 Open-Label Multi-Center Trial to Determine the Dosimetry and Safety of Technetium Tc99m Sestamibi in Pediatric Subjects

Objectives: To determine radiation absorbed doses, biodistribution in blood and urine (pharmacokinetics) and safety of Tc99m Sestamibi (at rest and stress) in two pediatric age groups

Study Design: Phase 1-2 open label non-randomized multicenter study to determine the dosimetry, pharmacokinetics (PK) and safety of Cardiolite in pediatric subjects who were scheduled to undergo a rest or stress Cardiolite single photon emission computed tomography (SPECT) Imaging study

Age groups studied:
4 years to < 12 years (children)
≥12 years to < 17 years (adolescents)

Number of patients and demographics
78 subjects imaged
39 children 4 years to < 12 years
39 adolescents ≥12 years to < 17 years

Rest: 13 children + 14 adolescents evaluated
Stress: 26 children + 25 adolescents evaluated

35 Asian, 31 white, 6 Black, 2 Native American, 4 other
Reviewer's comment: Kawasaki's Disease has the highest incidence in Asians, particular those of Japanese ancestry
47 subjects were evaluable for dosimetry

PK parameters studied
Blood AUC as % of injected dose
Terminal phase elimination half life
Mean residence time
Were obtained for each group, child-rest, child-stress. Adolescent-rest and adolescent-stress

Dosimetry and Pharmacokinetics Evaluation
Whole body scans were obtained at 15 minutes, 1.5 hours 4 hours and 8 hours. Regions of interest were drawn for appropriate organs. Time activity curves were obtained for the whole body, gall bladder, small intestine, upper and lower large intestine, heart wall, kidney, liver, salivary glands, spleen thyroid and urinary bladder. Using OLINDA software, mean radiation absorbed doses were obtained for the standard set of target organs using Christy-Eckerman pediatric phantoms
Organs that received the highest doses were as follows:
Upper large intestine.....0.30 rad/mCi
Small intestine.....0.16 rad/mCi
Gall bladder.....0.16 rad/mCi
Lower large intestine.....0.13 rad/mCi
Reviewer's comment: This dose distribution is consistent with elimination by the liver in the bile. This is consistent with the result that percent of injected dose in the liver was 26% at 15 minutes and 9% at 90 minutes. The corresponding numbers for stress subjects were 15% and 7% respectively

Effective dose equivalent .....0.072 rad/mCi

Safety Evaluation:
Incidence of AEs was :
Children.....28%
Adolescents.....10%
Overall.....19%
SAEs: Children .....1 (asthma), Adolescents 0 total 1
Except for 1 adolescent who had a clinically significant change in hematology parameters at 8 hours, there were no clinically significant changes in laboratory values

Study 2 (Protocol DuP 843-301)

A Phase III Open-Label Non-Randomized International Multicenter Trial to Evaluate the Efficacy and Safety of Cardiolite Myocardial Perfusion Imaging in Pediatric Subjects with Kawasaki Disease

Objectives: Primary
To determine the predictive value of Cardiolite rest and stress myocardial perfusion imaging to define a pediatric population with Kawasaki Disease at high and low risk of developing cardiac events
Secondary: To evaluate the safety of Cardiolite rest and stress MPI in pediatric subjects with KD requiring examination for cardiac ischemia

Study Design: Phase 3 open label non-randomized international multicenter study that enrolled pediatric subjects with Kawasaki disease (KD) scheduled to undergo invasive (angiography) or non-invasive (echocardiography or myocardial perfusion imaging (MPI)) cardiac testing to evaluate the presence of ischemic heart disease over a 22 month period (6 months analysis interim report)

Age groups studied:
4 years to < 12 years (children)
≥12 years to < 17 years (adolescents)

Patients enrolled and demographics
450 subjects enrolled
445 subjects were imaged with Cardiolite (safety population)
301 males, (68%) 144 females (32%)
Reviewer's comment: Kawasaki disease has a higher incidence in males than in females
329 children, 116 adolescents
Asian 275, White 135, Black 14, Native American 4, Hawaiian or pacific Islander 1, Other 16
20 patients had un-interpretable images
425 patients had evaluable stress MPI images and 6 month followup data (efficacy population)
51 patients had coronary angiography with available reports
45 subjects had abnormal Cardiolite scans (SSS (summed stress score) ≥ 4)
Reviewer's comment: Sin e, by definition, abnormality of the Cardiolite scan is determined by the SSS score only then the result or the rest scan is irrelevant)

Efficacy evaluation
Tc-99m Sestamibi images were read, at a core laboratory by 3 independent cardiologists with experience in reading nuclear perfusion images. Scans were read using a standard 17 segment model with each cardiac segment assigned a value of between 0 (normal perfusion) and 4 absent perfusion. The scores of all the segments were added to give a summed stress score (SSS) for stress image and summed rest score (SRS) for rest image. The summed difference score (SDS) is defined as the difference between the summed stress score and the summed rest score SDS = SSS-SRS. Scan results were compared to the occurrence of "Cardiac Events" defined as cardiac

death, MI, hospitalization due to cardiac etiology, heart failure or coronary intervention (CABG or angioplasty). Coronary angiogram reports for those subjects who had had coronary angiograms were evaluated by a consensus panel of 3 blinded cardiologists with the endpoint of greater than 50% obstruction of the vessel lumen being read as abnormal

The number of subjects with cardiac events during the first 6 months was very small, 3 events (0.6%) [one event each in 2 children and one event in an adolescent]
All three subjects had either a CABG or percutaneous coronary intervention within the 6 month period. There were no MIs CHF or cardiac deaths. All three subjects with cardiac events at 6 months had had a normal Cardiolite scan (SSS <. 4) Sensitivity, specificity, PPV and NPV calculated from these results are shown below

		Cardiac Event (truth)	
		YES	NO
SSS ≥ 4 (test)	YES	0	43
	NO	3	369

Sensitivity = 0, Specificity = 0.896
PPV = 0 NPV = 0.992

Reviewer's comment: The number of cardiac events in the 6 month period were too few to draw any firm conclusions with statistical significance. However, the fact that all three subjects who had a cardiac event had had a normal Cardiolite scan, does not support the hypothesis that an abnormal Cardiolite scan can be used as a predictor of cardiac events

51 subjects had available coronary angiography reports
11 of these had stenosis of ≥ 50%
For comparison with coronary angiography, an abnormal Cardiolite scan was defined as one with SDS > 2
Reviewer's comment: It is not entirely clear why the sponsor chose the summed stress score for comparison with cardiac outcomes and the summed difference score for comparison with coronary angiography
2 of the 11 subjects with stenosis also had SDS>2

.
Sensitivity = 0.18, Specificity = 0.75
PPV = 0.17, NPV = 0.77

Safety Evaluation: 445 subjects were exposed to Cardiolite. Most subjects had one-day rest-stress studies
There were no deaths
There was 1 SAE A patient was overdosed due to an incorrect calculation of dose There were no clinical signs or symptoms
Overall incidence of AEs was 9%

Most common AEs were headache and nausea . all nausea cases occurred in children
Mean changes in laboratory values from before dosing to 2-6 hours after dosing were not clinically significant
Rest vital signs remained stable for 30 min post injection
Vital sign changes during exerciser were consistent with changes caused by exercise alone
Abnormalities in EKGs were noted in 7% of subjects before Cardiolite injection and in 7% after Cardiolite injection changes were not clinically significant
During exercise, heart rate increased, RR interval shortened, Pr shortened slightly, QRS remained unchanged QT shortened slightly. After peak exercise and injection of Cardiolite Parameters returned slowly to normal

Sponsor states that there were no statistical issues and that no covariate analysis was conducted due to the very small number of events. In evaluating the predictive value of the MPI scans sensitivity, specificity PPV and NPV were calculated. In comparing MPI and angiography results sensitivity, specificity PPV and NPV were calculated.

Study 3 (Protocol DuP 843-302}

Objective: to evaluate the performance (sensitivity and specificity) of Cardiolite MPI relative to coronary angiography in pediatric KD patients. To evaluate the safety of Cardiolite rest-stress, stress-rest or stress only SPECT MPI in pediatric KD patients.

Phase 3 retrospective case history international multicenter study of pediatric Kawasaki disease patients who completed rest-stress, stress-rest or stress only Cardiolite SPECT myocardial perfusion imaging (MPI) within 10 years of June 30, 2006, and who have had coronary angiography within ± 3 months of the Cardiolite scan

428 patients screened
86 patients had had coronary angiography within 90 days of Cardiolite scan and were analyzed for safety
85 patients had evaluable angiographic images
14 patients had abnormal angiograms
72 patients had both evaluable Cardiolite scans and evaluable angiographic images
12/72 had abnormal angiograms ≥ 50% stenosis
3/72 had abnormal Cardiolite scans (SSS ≥ 4)
1 patient had both an abnormal angiogram and an abnormal Cardiolite scan

		Angiogram	
MPI		Pos	Neg
	Pos	1	2
	Neg	11	58

Sensitivity = 0.08 Specificity = 0.97
NPV = 0.84

6 Review of Efficacy

Efficacy Summary

Indication

Current indication in Current package insert: Cardiolite kit for the preparation of Technetium 99mTc Sestamibi injection is a myocardial perfusion agent that is indicated for detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and myocardial infarction (non-reversible defects) in evaluating myocardial function and developing information for use in patient management decisions. Cardiolite evaluation of myocardial ischemia can be accomplished with rest and cardiovascular stress techniques

Reviewer's comment: Adults referred for Cardiolite myocardial perfusion imaging almost invariably have atherosclerotic coronary disease. Atherosclerotic coronary artery disease is found in the geriatric age group and does not exist in children. The current submission includes three clinical studies of Cardiolite myocardial rest and stress imaging of pediatric patients with Kawasaki disease. The sponsor has not requested an additional indication for myocardial perfusion imaging of such patients

Methods

Efficacy was evaluated in two Phase 3 studies, DuP 843-301 and DuP 843-302. Study DuP 843-301 is a Phase 3 **prospective** study using the ability of Cardiolite scans to predict the occurrence of cardiac events as the standard of truth for efficacy evaluation. A secondary efficacy analysis uses coronary angiograms as the standard of truth in the subset of patients who have had coronary angiograms within ± 90 days of the Cardiolite scan. Study DuP 843-302 is a Phase 3

retrospective case history study of patients who have had a coronary angiogram within ± 90 days of a Cardiolite myocardial perfusion scan using coronary angiography as a standard of truth
Reviewer's comment: Because study 301 was a prospective study and 302 was a retrospective study and because both the standard of truth and the definition of a positive Cardiolite scan were different in the two studies, data from these two studies can not be combined in a single dataset for analysis, but data from each study must be analyzed separately

Demographics

Study DuP 843-301

450 subjects enrolled
445 subjects were imaged with Cardiolite (safety population)
301 males, (68%) 144 females (32%)
329 children, 116 adolescents
Asian 275, White 135, Black 14, Native American 4, Hawaiian or pacific Islander 1, Other 16
20 patients had un-interpretable images
425 patients had evaluable stress MPI images and 6 month followup data (efficacy population)
51 patients had coronary angiography with available reports
45 subjects had abnormal Cardiolite scans (SSS (summed stress score) ≥ 4)

Study DuP 843-302

428 patients with Tc99m Sestamibi scans screened,
86 patients had coronary angiography within 90 days of Cardiolite scan and were analyzed for safety

Patient Disposition

Study DuP 843-301
20 of 445 imaged patients had un-interpretable images
425 patients had evaluable stress MPI images and 6 month followup data (efficacy population)
51 patients had coronary angiography with available reports
45 subjects had abnormal Cardiolite scans (SSS (summed stress score) ≥ 4)

Study DuP 843-302
86 patients had coronary angiography within 90 days of Cardiolite scan and were analyzed for safety
72 patients had both evaluable Cardiolite scans and evaluable angiographic images (primary efficacy population)

Analysis of Primary Endpoint(s)

Study DuP 843-301

The primary efficacy endpoint of study 301 was the sensitivity and specificity of Cardiolite scans using the occurrence of a cardiac event at 6 months post scan as the standard of truth

Scans were read in accord with a standard 17 segment cardiac model by three blinded readers at a core laboratory. Stress and rest scans were read according to a standard 17 segment model with each cardiac segment being assigned a number between 0 (normal perfusion) to 4 (absent perfusion). The scores for all 17 segments were added to give a summed stress score (SSS) for the stress images and a summed rest score (SRS) for the rest images. The summed difference score (SDS) was defined as SDS = SSS-SRS. For the purposes of this study an abnormal Cardiolite scan was defined as a scan with SSS $\geq$ 4. A cardiac event was defined as cardiac death, MI, hospitalization due to cardiac etiology, heart failure or cardiac intervention (CABG or angioplasty).
The number of subjects with abnormal Cardiolite scans was 45. There was good agreement between readers of the Cardiolite scans with agreement rates between any two readers of approximately 91%. The number of subjects with cardiac events during the first 6 months was very small, 3 events (0.6%) [one event each in 2 children and 1 adolescent]
All three subjects had either a CABG or percutaneous coronary intervention within the 6 month period. There were no MIs, CHF, or cardiac deaths (hard cardiac events). All three subjects with cardiac events had had a normal SSS.

		Cardiac Event	
SSS >4		YES	NO
	YES	0	43
	NO	3	369

Sensitivity = 0, Specificity = 0.896
PPV = 0 NPV = .992
(ISE table 4 p30)

Reviewer's comment: The number of cardiac events in the 6 month period were too few to draw any firm conclusions. However, the fact that all three subjects who had a cardiac event had had a normal SSS, does not support the hypothesis that an abnormal SSS can be used as a predictor of cardiac events

Study DuP 843-302

The primary efficacy endpoint of study 302 was the sensitivity and specificity of Cardiolite scans using coronary angiography as the gold standard

Medical records of patients with known or suspected classical or incomplete Kawasaki's disease

were screened for enrollment. The search covered a 10 year period prior to the initiation of the protocol on June 30, 2006. Studies from patients who have undergone rest and stress or stress only Tc 99m Sestamibi MPI studies and who have had x-ray angiography within ± 3 months of the MPI study, were sent to a core laboratory for evaluation. Both exercise and pharmacological stress procedures were acceptable. Medical records were carefully reviewed and a plan for the collection and evaluation of adverse events that occurred within 3 days after the MPI procedure was provided. Demographic, medical history and vital signs data were also be collected
Statistical analysis were done on images from patients who have had both stress and rest MPI and angiography within ± 3 months of MPI scan
Efficacy Evaluation: Cardiolite scans were read by three board certified nuclear cardiologists using a 17 segment model as described by the independent review charter. Angiograms were read by a single board certified Cardiologist
A positive Cardiolite scan was defined as summed stress score (SSS) ≥ 4. A positive angiogram was defined as ≥ 50% stenosis in at least 1 coronary artery. 12 patients had positive angiograms with ≥ 50% stenosis One of the 12 had an abnormal Cardiolite scan (SSS ≥ 4) and the other 11 had normal Cardiolite scans.

		Angiogram	
MPI		Pos	Neg
	Pos	1	2
	Neg	11	58

Sensitivity = 0.08 (CI, 0 - 0.38)
Specificity = 0.97 (CI, 0.88 - 1.0)
NPV = 0.84, PPV = 0.33
(ISE p 46-47)

Analysis of Secondary Endpoints(s)

Study DuP 843-301

In Study 302, the secondary efficacy endpoint was sensitivity and specificity of the Cardiolite scans using coronary angiography as the standard of truth in those subjects who had coronary angiograms within ± 90 days of the Cardiolite scan
51 subjects had available coronary angiography reports
11 of these had stenosis of ≥ 50%
For comparison with coronary angiography, an abnormal Cardiolite scan was defined as one with SDS > 2
51 subjects had available coronary angiography reports
11 of these had stenosis of ≥ 50%
For comparison with coronary angiography, an abnormal Cardiolite scan was defined as one with SDS > 2

Reviewer's comment: It is not entirely clear why the sponsor chose the SSS > 4 for comparison with cardiac outcomes and the SDS > 2 for comparison with coronary angiography. In study 302 the sponsor chose SSS > 4 for comparison with coronary angiography.
2 of the 11 subjects with stenosis of ≥ 50% also had SDS > 2. and 9 had SDS ≤ 2
Of the 40 patients stenosis < 50%, 10 had SDS >2 and 30 had SDS ≤ 2

		stenosis of ≥ 50%	
SDS >2		Yes	No
	Yes	2	10
	No	9	40

Sensitivity = 0.18, Specificity = 0.75
PPV = 0.17, NPV = 0.77
(ISE table 4.7 p 18)
Reviewer's Comment: although the same gold standard (coronary angiography) was used for the primary efficacy endpoint of study 302 and for the secondary endpoint for study 301, these results can not be compared because different definitions of positive Cardiolite scans were used in the 2 cases, SDS > 2, for the secondary endpoint of 301 and SSS ≥ 4 for the primary efficacy endpoint of 302. SSS is a measure of all perfusion defects, SRS is a measure of irreversible perfusion defects and therefore SDS is a measure of reversible perfusion defects

Other Endpoints

Subpopulations

Subpopulations studied in study 201
Age groups studied:
4 years to < 12 years
≥12 years to < 17 years
Number of patients and demographics
78 subjects imaged
39 children 4 years to < 12 years
39 adolescents ≥12 years to < 17 years
Rest: 13 children + 14 adolescents evaluated
Stress:
35 Asian, 31 white, 6 Black, 2 Native American, 4 other
Reviewer's comment: Kawasaki's Disease has the highest incidence in Asians, particular those of Japanese ancestry ands also has a higher incidence in males than females
Separate subgroup analyses of pharmacokinetic and dosimetry data were not performed in study 301

Subpopulations studied in study 301
Age groups studied:
4 years to < 12 years (children)

≥12 years to < 17 years (adolescents)

Patients enrolled and demographics
450 subjects enrolled
445 subjects were imaged with Cardiolite (safety population)
301 males, (68%) 144 females (32%)
329 children, 116 adolescents
Asian 275, White 135, Black 14, Native American 4, Hawaiian or pacific Islander 1, Other 16
20 patients had un-interpretable images
425 patients had evaluable stress MPI images and 6 month followup data (efficacy population)
51 patients had coronary angiography with available reports
45 subjects had abnormal Cardiolite scans (SSS ≥ 4)

Subpopulations studied in study 302
In study 302, all patients were included in a single age group
Age group studied
1 month to < 17 years
Number of Patients:
428 patients with Tc99m Sestamibi scans screened
86 patients had had coronary angiography within 90 days of Cardiolite scan and were analyzed for safety
85 patients had evaluable angiographic images
14 patients had abnormal angiograms
72 patients had both evaluable Cardiolite scans and evaluable angiographic images
12/72 had abnormal angiograms ≥ 50% stenosis
3/72 had abnormal Cardiolite scans (SSS ≥ 4)
1 patient had both an abnormal angiogram and an abnormal Cardiolite scan
Separate subgroup analyses of efficacy seta were not performed in study 302

Analysis of Clinical Information Relevant to Dosing Recommendations

Only a single dosing regimen was used in these studies. Efficacy was not demonstrated for the dosing regimen studied

Discussion of Persistence of Efficacy and/or Tolerance Effects

No efficacy was demonstrated in either clinical trial 301 or 302. The issue of the persistence of efficacy is moot
l Efficacy Analyses
The current standard of care in monitoring patients with Kawasaki disease who are at risk for cardiac sequelae is periodic evaluation with coronary angiography and/or cardiac ultrasound. Coronary angiography is an invasive procedure with significant morbidity and mortality. If the

non-invasive Cardiolite scan could be shown to provide the same information as coronary angiography the re would be a significant clinical benefit. However, in both clinical studies, 301 and 302 Cardiolite scanning was shown to have a very low sensitivity. In study 301, using cardiac events at 6 months, sensitivity was 0 and using coronary angiography as a gold standard in those patients who had angiography within 6 months of Cardiolie scanning the sensitivity was 0.08. In study 302 using coronary angiography as a gold standard, the sensitivity was 0.18. A diagnostic test with a sensitivity below 0.5 (coin toss) would have no clinical utility

7 Review of Safety

Safety Summary

Methods

Clinical Studies Used to Evaluate Safety

Study 1 (Protocol DuP 843-201): Pediatric Radiation Dosimetry Determination and Pharmacokinetic (Biodistribution) Study

Study 2 (Protocol DuP 843-301): Pediatric Diagnostic Efficacy and Safety Study (Prospective Study)

Study 3 (Protocol DuP 843-302): Pediatric Diagnostic Efficacy and Safety Study (Retrospective Study)

Adequacy of Safety Assessments

Protocol DuP 843-201: Was a small pharmacokinetics/biodistribution/dosimetry study with 78 subjects
Protocol DuP 843-302 was a retrospective Phase 3 safety and efficacy study. No prospective plan for safety monitoring and monitoring of adverse events was possible in this study

Protocol DuP 843-301 was the only prospective Phase 3 study in this submission, with a population analyzable for safety of 445 subjects.

A total of 523 subjects were analyzable for safety, 78 (15%) from study 201 and 445 (85%) from study 301

There were no pre-clinical safety studies performed on immature animals

Pooling Data Across Studies to Estimate and Compare Incidence

The sponsor has not pooled data from the three studies in the integrated summary of safety. Data from the retrospective study, 302 , could not be pooled with safety data from the prospective studies, 201 and 301

Pooled analysis of safety data

The sponsor, in the integrated summary of safety (ISWS) did not perform a pooled analysis of safety data from the three studies

Reviewer's comment: In studies 201 and 301 the same demographic groups of subjects were imaged using the same dosing regimen. The fact that in 201 pharmacokinetics and in 301 efficacy was assessed, should not have affected the analysis of safety. In principle a pooled safety analysis of the data from 201 and 301 could have been performed. Study 302 was an international, multi-center retrospective study of subjects imaged over a 10 year period. There was of course no prospective plan for patient safety monitoring and monitoring varied from institution. Dosing was in accordance with individual institutional protocol and also varied. Many adverse events may not have been recorded in the patient record. Thus it would not only be difficult to integrate data from 302 with data from the other two studies, but it would also be difficult to perform a meaningful safety analysis of study 302 itself. Study 201 was a relatively small dosimetry/pharmacokinetics study with 39 children and 39 adolescents for a total subject population of 78. Study 301 was a larger phase 3 study with 328 children and 116 adolescents for a total of 444 subjects. Thus, the principal safety analysis will be based on data from a single Phase 3 study

Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Target populations:
Pediatric patients with Kawasaki disease
4 years to < 12 years (children)
≥12 years to < 17 years (adolescents)
Study 201, 78 subjects
Study 301, 445 subjects
Dosing:
Rest and stress scans were obtained either on the same day or on two consecutive days. Doses of Cardiolite dosing was different in the two cases
Studies 201 and 301

1 One day protocol 0.1 - 0.2 mCi/kg IV for first dose (rest imaging), 0.3mCi/kg IV second dose (stress imaging)
2 .Two day protocol 0.2 mCi/kg IV each for both rest and stress imaging

Study 302 was an international retrospective study. Dosing was according to institutional imaging protocol at the time of imaging

Explorations for Dose Response

There were no clinical dose-ranging studies
Only a single dosing regimen was used in studies 201 and 301:

3 One day protocol 0.1-0.2 mCi/kg IV for first dose (rest imaging), 0.3mCi/kg IV second dose (stress imaging0
4 .Two day protocol 0.2 mCi/kg IV each for both rest and stress imaging

The sponsor has provided no specific justification for this dose prescription

Study 302 was a retrospective study so no prospective dose prescription was possible
There were no dose-ranging studies in this submission

Special Animal and/or In Vitro Testing

Pre-clinical safety studies in immature animal were not performed

Major Safety Results

Deaths

There were no deaths reported in any of the three studies

Nonfatal Serious Adverse Events

Study 201: A 7 year old Black female with a history of allergies developed asthma after a 1 day stress/rest Cardiolite scan. She was treated with prednisone and resolved without further treatment. This event was considered by the investigator unlikely to be related to the drug
Study 302: A 5 year old female was overdosed with Cardiolite when a technician calculated the dose on the basis of her weight in pounds instead of kilograms. She received 16.9 mCi when she should have received 7.7 mCi. She experienced no signs or symptoms and was given no treatment. This AE was caused by a technician error and not by the drug

Dropouts and/or Discontinuations

Study 201: In one subject the drug partially infiltrated and a scan was not obtained. He was discontinued from the study
Study 301: No discontinuations due to AEs were reported

Significant Adverse Events

Except for SAEs and discontinuations, adverse events, adverse events are neither tabulated or discussed in the ISS

Submission Specific Primary Safety Concerns

Because mass doses are sub-pharmacological and radiation absorbed doses are orders of magnitude below organ tolerance doses diagnostic radiopharmaceutical agents are generally safe

Supportive Safety Results

Cardiolite is currently marketed for myocardial perfusion scanning in adult patients with atherosclerotic coronary disease and post marketing safety data are available

Common Adverse Events

In adults undergoing cardiac scanning the most common adverse events were Special senses (7.3%) and taste perversion (7.1%)

Laboratory Findings

No clinically significant changes in laboratory findings have been reported

Vital Signs

Changes in vital signs in subjects undergoing exercise stress imaging were consistent with changes produced by exercise

Electrocardiograms (ECGs)

EKG changes in subjects undergoing exercise stress scanning were consistent with the effects of exercise

Special Safety Studies

This submission contains no reports of any special safety studies

Immunogenicity

One subject in study 201, with a history of allergies did develop asthma which the sponsor maintains was not drug related

Other Safety Explorations

Dose Dependency for Adverse Events

All subjects were imaged with the same dosing regimen. Dose dependency of adverse events was not studied

Time Dependency for Adverse Events

Time dependency of adverse events is not discussed by the sponsor in this submission

Drug-Demographic Interactions

Since Kawasaki disease is most common in males of Japanese ancestry, the largest group in the study were Asian males. No differences in safety or efficacy of Cardiolite between ethnic groups were noted

Drug-Disease Interactions

No data on drug disease interactions were contained in this submission

Drug-Drug Interactions

No data on drug-drug interactions was contained in this submission

Additional Safety Explorations

Human Carcinogenicity

There was no genotoxicity data in this submission. Radiation is generally believed to be both carcinogenic and genotoxic even in very small doses

Human Reproduction and Pregnancy Data

Most subjects in these studies have below reproductive age. No data on the effect of Cardiolite on Reproduction has been submitted

Pediatrics and Effect on Growth

The effect on growth has not been studied

Overdose, Drug Abuse Potential, Withdrawal and Rebound

One subject in study 201 received an overdose of Cardiolite (2.2 times the required dose since dose was calculated on the basis of the patient's weight in pounds rather than kilograms) due to technician error. The subject experienced no signs or symptoms and no treatment was required The drug is a diagnostic radiopharmaceutical administered IV in sub-pharmacological doses under the direction of a physician. There is no potential for drug abuse. Since drug is given on a one time basis there is no potential for withdrawal or rebound effects

Safety assessment

Diagnostic radiopharmaceuticals are generally considered safe because of the low radiation absorbed doses delivered to normal tissues are orders of magnitude below organ tolerance doses(see pharmacokinetics and dosimetry sections of this review), and because mass doses of ligand are sub pharmaceutical. These conclusions are supported by data from the pediatric clinic al studies and from the adult post-marketing experiences. In both pediatric studies there were a total of 2 serious adverse events, neither of which could be definitely attributed to the drug. The most common non-serious adverse events were taste perversion and special senses. Changes in vital signs and EKG changes were noted during exercise stress imaging but these were consistent with the effects of exercise

8 Postmarketing Experience

According to the sponsor there has been a considerable amount of off-label use of Cardiolite for cardiac perfusion imaging of pediatric subjects with Kawasaki disease. The sponsor has provided no discussion of any safety issues raised by this off-label experience

9 Appendices

Labeling Recommendations:

Since efficacy was not demonstrated for the pediatric population with Kawasaki disease no pediatric efficacy data should be added to the label. However pediatric safety, pharmacokinetics and dosimetry data should be included in the label in the "Pediatric Use" section.

[redacted]

[redacted]

[redacted]

[redacted]

Table 3.0 Estimated Radiation Absorbed Dose in Adolescents and Children from CARDIOLITE®

	REST			
	Child (4 - 12 years)		Adolescent (13-16 years)	
Organ	rem/mCi	mSv/MBq	rem/mCi	mSv/MBq
Adrenals	0.032	0.0087	0.024	0.0064
Brain	0.0082	0.0022	0.0059	0.0016
Breasts	0.010	0.0028	0.0073	0.0020
Gallbladder Wall	0.23	0.061	0.14	0.039
Lower Large Intestine Wall	0.20	0.054	0.10	0.027
Small Intestine	0.25	0.069	0.14	0.038
Stomach	0.040	0.0109	0.027	0.0074
Upper Large Intestine	0.43	0.12	0.29	0.079
Heart Wall	0.039	0.011	0.032	0.009
Kidneys	0.10	0.027	0.081	0.022
Liver	0.069	0.019	0.049	0.013
Lungs	0.034	0.0091	0.027	0.0072
Muscle	0.021	0.0057	0.015	0.0039
Ovaries	0.091	0.025	0.059	0.016
Pancreas	0.042	0.011	0.028	0.0077
Red Marrow	0.038	0.0103	0.029	0.0079
Bone Surfaces	0.047	0.013	0.035	0.010
Salivary Glands	0.033	0.0089	0.017	0.0046
Skin	0.010	0.0027	0.0066	0.0018
Spleen	0.052	0.014	0.043	0.012
Testes	0.018	0.0049	0.010	0.0028
Thymus	0.012	0.0033	0.010	0.0026
Thyroid	0.027	0.0072	0.020	0.0053
Urinary Bladder Wall	0.14	0.038	0.074	0.020
Uterus	0.078	0.021	0.047	0.013
Total Body	0.028	0.007	0.019	0.005
Effective Dose	0.076	0.020	0.047	0.013
Effective Dose Equivalent	0.10	0.027	0.064	0.017

	STRESS			
	Child (4 - 12 years)		Adolescent (13-16 years)	
Organ	rem/mCi	mSv/MBq	rem/30mCi	mSv/1110MBq
Adrenals	0.036	0.0096	0.022	0.0059
Brain	0.015	0.0039	0.0088	0.0024
Breasts	0.015	0.0040	0.0093	0.0025
Gallbladder Wall	0.16	0.044	0.10	0.026
Lower Large Intestine Wall	0.13	0.036	0.086	0.023
Small Intestine	0.17	0.045	0.088	0.024
Stomach	0.041	0.011	0.024	0.0065
Upper Large Intestine	0.34	0.092	0.17	0.047
Heart Wall	0.052	0.014	0.037	0.010
Kidneys	0.10	0.028	0.060	0.016
Liver	0.064	0.017	0.036	0.010
Lungs	0.042	0.011	0.028	0.0075
Muscle	0.024	0.0064	0.015	0.0040
Ovaries	0.072	0.019	0.044	0.012
Pancreas	0.043	0.012	0.025	0.0068
Red Marrow	0.024	0.0066	0.019	0.0050
Bone Surfaces	0.051	0.014	0.036	0.010
Salivary Glands	0.026	0.0072	0.011	0.0029
Skin	0.013	0.0036	0.0080	0.0022
Spleen	0.051	0.014	0.033	0.0089
Testes	0.022	0.0059	0.013	0.0035
Thymus	0.019	0.0053	0.013	0.0035
Thyroid	0.042	0.011	0.022	0.0059
Urinary Bladder Wall	0.13	0.034	0.074	0.020
Uterus	0.065	0.018	0.038	0.010
Total Body	0.029	0.008	0.018	0.0048
Effective Dose	0.064	0.017	0.037	0.010
Effective Dose Equivalent	0.082	0.022	0.045	0.012

Radiation dosimetry calculations performed using OLINDA/EXM by CDE Dosimetry Services, Oak Ridge, TN

Adverse reactions in pediatric population:

Adverse events were evaluated in 609 pediatric subjects (children and adolescents) treated with CARDIOLITE® from three clinical studies (201, 301, 302). Of these 609 pediatric subjects, 414 (68%) subjects were male and 195 (32%) subjects were female. A total of 60 (10%) subjects reported at least one adverse event of any severity. There was one case of CARDIOLITE® overdose considered to be serious adverse event with no symptoms and there was one case of asthma considered serious and related to study drug by the investigator. Adverse events occurring at a rate of 0.5% or greater after CARDIOLITE® administration are nausea, chest pain, skin and subcutaneous tissue disorders, and headache.

Advisory Committee Meeting

No advisory committee meetings are planned

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/s/

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4/10/2008 09:00:42 AM
MEDICAL OFFICER

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