Office of Clinical Pharmacology Review

NDA Number	020351
Link to EDR	\\CDSESUB1\evsprod\NDA020351\020351.enx
Submission Date	October 5, 2016; SDN 303
Submission Type	Efficacy Supplement; PLR conversion
Brand Name	Visipaque™
Generic Name	Iodixanol
Dosage Form and Strength	Injectable solution. The current efficacy supplement is exclusively for the 320 mg I concentration.
Route of Administration	Intravenous (for proposed indication)
Dosing Regimen	70-80 mL main bolus volume at a flow rate of (b) (4) mL/s, followed by 20 mL saline flush
Indication (s)	**Approved Indications:** **INTRA-ARTERIAL** VISIPAQUE Injection (270 mgI/mL) is indicated for intra-arterial digital subtraction angiography. VISIPAQUE Injection (320 mgI/mL) is indicated for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography. **INTRAVENOUS** VISIPAQUE Injection (270 mgI/mL) is indicated for CECT imaging of the head and body, excretory urography, and peripheral venography. VISIPAQUE Injection (320 mgI/mL) is indicated for CECT imaging of the head and body, and excretory urography. **Proposed New Indication (in red):** Visipaque Injection (320 mgI/mL) is indicated for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.
Applicant	GE Healthcare
Associated IND/NDA	IND 34,585 and NDA 20-808
OCP Review Team	Christy S John, Ph.D., Gene Williams, Ph.D.

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1. EXECUTIVE SUMMARY

Visipaque is approved for intra-arterial administration for angiography and angiocardiography, and for intravenous administration for CT of the head and body, excretory urography and peripheral venography. GE Healthcare proposes to add a new indication for the use of Visipaque Injection (320 mgI/mL) for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease. CCTA is a procedure in which images are acquired during the arterial phase of contrast enhancement in order to visualize the coronary arteries. The current efficacy supplement is exclusively for the 320 mg I concentration.

There are no pharmacokinetics or drug interaction data in the submission.

To support the new indication the applicant has conducted two clinical studies: GE-189-002/GE012-101 and GE012-096. The standard of truth (SoT) for GE-012-101 was invasive coronary angiography for many patients, whereas Study GE-012-096 used clinical outcomes as a SoT. The sensitivity for the two studies were 90, 90, 98% for three different readers for Study GE012-101 and 90% Study GE-012-096. The specificity for Study GE-012-101 was 70, 76, 81% for three different readers and 87% for Study GE-012-096. This data suggested that Visipaque CCTA can assist in the diagnostic evaluation of patients with suspected coronary artery disease.

No dose finding data was acquired to support the CCTA indication. The recommended dosing is based on clinical studies conducted by applicant, published literature on CCTA, and guidelines from The Society of Cardiovascular Computed Tomography (SCCT) and The American College of Radiology (ACR).

1.1 Recommendations

From the clinical pharmacology perspective this supplemental NDA is approvable provided an agreement can be reached on labeling.

1.2 Post-Marketing Requirements and Commitments

From the Clinical Pharmacology perspective no post-marketing requirements or commitments are indicated.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

There are no pharmacokinetics or drug interaction data in the submission.

Visipaque™ (iodixanol) is a dimeric, isosmolar, nonionic, water-soluble, radiographic contrast medium with a molecular weight of 1550 Dalton (iodine content 49%). It is available as a ready-to-use sterile solution for IV injection in two concentrations (270 mgI/mL and 320 mgI/mL). Intravascular injection of iodixanol opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

The following is excerpted from the approved package insert, "The degree of enhancement, following administration of Visipaque Injection, is directly related to the iodine content in an administered dose with peak iodine plasma levels occurring immediately following intravascular injection. Iodine plasma levels fall rapidly within 5 to 10 minutes. Contrast enhancement with Visipaque Injection is greatest immediately after bolus injections (15 seconds to 120 seconds). Thus, greatest enhancement may be detected by a series of consecutive 2- to 3-second scans performed within 30 to 90 seconds after injection (i.e., dynamic computed tomographic imaging).

In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution was 0.26 L/kg body weight (b.w.), consistent with distribution to extracellular space. Iodixanol metabolites have not been demonstrated. Measurements of plasma and urine levels suggest that body clearance of iodixanol is primarily due to renal clearance. In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within 5 days post-injection. ″

2.2 Dosing and Therapeutic Individualization

The applicant has proposed dosing of Visipaque for the CCTA indication be based on their clinical experience, published literature [Bae K.T. Radiology Vol 256, 33-51, 2010], and the recommendations of professional organizations such as The Society of Cardiovascular Computed Tomography (SCCT) guidelines for performance of coronary computed tomographic angiography [Abbara et al. Journal of Cardiovascular Computed Tomography, Vol 3, 190-204, 2009] and The American College of Radiology (ACR). **Table 1.** summarizes these sources.

Table 1. Comparison of CCTA Contrast Dosing and Injection Parameters

Recommendation	GE-189-002	GE-012-096	[Bae 2010]	SCCT [Abbara et al. 2009]	ACR [ACR 2014]
Concentration mgI/mL	320	320	320-370	High	>300
Rate in seconds	4-5 mL	According to facility guidelines	4-5 mL	4-7 mL	>3-5 mL
Volume	70-80 mL	30-180 mL (mean 91.5 mL)	75-100 mL	Typically 50-120 mL	None
Criteria for the selection of contrast volume	Selected by the investigator	According to facility guidelines	Injection rate and scan duration	Injection rate and scan duration	Weight
Biphasic, Multiphasic or both?	Both	According to facility guidelines	Both	Both	Biphasic preferred
Recommended Iodine delivery rate (g I/s)	1.28-1.6	According to facility guidelines	1.28-1.6	None	None
Optimal attenuation in coronaries	Not measured	Not measured	300-350 HU	>250	None
Test bolus, bolus tracking or both?	Test bolus	According to facility guidelines	Both	Both	Both

No individualization of dose has been studied. The applicant recommends a dose of 1 ml/kg, not to exceed 150 mL, for patients >80 kg/mL. Both weight-based and fixed volume dosing have been used in published studies of CCTA [Nakaura et al. Investigative Radiology, 43, 512-519, 2008; Komatsu et al. Journal of Cardiology, 61, 155-161, 2013]. Nakaura et al. studied software-tailored contrast injections based on patient weight and compared them to a fixed-volume control group using 75 mL at 7.2 mL per second with no adjustments made for weight. Comparable image noise and quality were found between both groups. Nakaura et al. also compared patient weight-adjusted and fixed iodine protocols. Patients in both groups received contrast at a concentration of 370 mgI/mL. The fixed dose group received 80 mL at 4 mL/second (i.e., a constant injection duration of 20 seconds) while the weight-adjusted group received 1.0 mL/kg with injection rate adjusted to achieve an injection duration of 15 seconds. This study showed that, using qualitative scoring, beam hardening artifacts were higher in the fixed volume dose group but the level of enhancement in the coronaries was similar for both groups.

Clinical pharmacology agrees the applicant's proposed dosing recommendations, with the exception that we recommend that an option for weight-based dosing – for all patients, not only patients of large body weight – be added to the package insert dosing table.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

There are no pharmacokinetics or drug interaction data in the submission. Regarding the new indication for CCTA, clinical pharmacology recommends edits to the dosing table that the applicant proposes for the package insert, including the addition of an option for weight-based

dosing. As part of the review of the new PLR format, edits to sections 7, 8 and 12 are also recommended. These recommendations were incorporated during internal meetings with the clinical division (the Division of Medical Imaging Products: DMIP). The revised package insert has yet to be conveyed to the applicant for negotiation. The applicant's annotated proposed package insert (from the initial submission), and FDA's currently proposed version, are attached to this review as appendices (**Appendix 1** and **Appendix 2**, respectively).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Visipaque 320 mgI/mL was first approved for intra-arterial (IA) use in February 1993 and for intravenous use in 1994. Visipaque is approved in the United States for IA administration for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography and for IV administration for contrast-enhanced CT imaging of the head and body, and excretory urography.

The regulatory guidance from the FDA regarding the coronary CTA indication began in 2009 and continued through 2016, as summarized in **Table 2.**

Table 2. Regulatory History

Date	Application	Description
8/27/2009	IND 034585	Meeting minutes (3/22/2009) from face-to-face meeting regarding sponsor's submitted clinical trial results. FDA concluded "given the inadequacy of the reviewed study data to form the basis for an approvable NDA submission, FDA recommends that additional pivotal studies are needed to support the use of Visipaque as an imaging agent in CCTA for diagnosis and exclusion of CAD."
6/16/2015	IND 034585	Sponsor submitted correspondence requesting a meeting to discuss Phase 3 study design and clinical program to support a coronary CTA indication for Visipaque
11/10/2015	IND 034585	Face-to-face meeting for re-positioning of sponsor's request based on newly available information and guidelines. The sponsor-proposed Phase 3 study was deemed unnecessary by FDA. FDA suggested a future pre sNDA meeting for presentation of the relevant studies and publications.
5/13/2016	IND 034585	Pre-sNDA meeting requested by sponsor to discuss the studies

3.2 General Pharmacology and Pharmacokinetic Characteristics

The following information is adapted from the approved package insert.

Iodixanol is a dimeric, isosmolar, nonionic, water soluble, iodinated x-ray contrast agent for intravascular administration. Intravascular injection of iodixanol opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

Pharmacokinetics

Distribution
In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution was 0.26 L/kg body weight, consistent with distribution to extracellular space.

Elimination
Plasma and urine levels suggest that body clearance of iodixanol is primarily due to renal clearance. In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within five days post-injection. In 40 healthy, young male volunteers receiving a single intravenous administration of VISIPAQUE Injection in doses of 0.3 to 1.2 gI/k body weight, the elimination half-life was 2.1 h (± 0.1); and renal clearance was 110 mL/min (±14), equivalent to glomerular filtration (108 mL/min). These values were independent of the dose administered.

Metabolism
Iodixanol metabolites have not been demonstrated.

Pharmacokinetics in Special Populations
Renal Impairment:
In patients with significantly impaired renal function, the total clearance of iodixanol is reduced and the half-life in plasma phase is prolonged. In a study of 16 adult patients who were scheduled for renal transplant, the elimination of iodixanol 320 mgI/mL was studied. The patients' baseline mean creatinine levels were 6.3 mg/dL (±1.5) and mean creatinine clearances were 13.61 mL/min (±4.67). In these patients, the plasma half-life was increased to 23 hours (normal t1/2 = 2 hours). In these patients, levels of iodixanol were detected 5 days after dosing. Contrast enhancement time in kidneys increased from 6 hours to at least 24 hours.

Pediatric:
Comparing to adult half-life which is approximately 2 h, the half-life in children <12 years of age range from 2.3 to 4 h, being longer in newborn and children <2 months). Pharmacodynamic dose adjustments to account for differences in elimination half-life in pediatric patients <6 months of age have not been studied.

Pharmacodynamics

As with other iodinated contrast agents, following administration of Visipaque injection, the degree of enhancement is directly related to the iodine content in an administered dose. The peak iodine plasma levels occur immediately following rapid intravascular injection. Iodine plasma levels fall rapidly within 5 to 10 minutes.

The greatest enhancement may be detected by a series of consecutive two-to-three second scans performed within 30 to 90 seconds after injection (i.e., dynamic computed tomographic imaging). Iodinated contrast agents may be visualized in the renal parenchyma within 30-60 seconds following rapid intravenous injection. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1-3 minutes, with optimum contrast occurring within 5-15 minutes. In normal brain with an intact blood-brain barrier, contrast enhancement is generally due to the presence of iodinated contrast agent within the intravascular space.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

There are no pharmacokinetics or dose-response data in CCTA patients to support the CCTA indication.

To support the new indication the applicant has conducted two clinical studies: GE-189-002/GE012-101 and GE012-096. The standard of truth (SoT) for GE-012-101 was invasive coronary angiography for many patients, whereas Study GE-012-096 used clinical outcomes as a SoT. The sensitivity for the two studies were 90, 90, 98% for three different readers for Study GE012-101 and 90% Study GE-012-096. The specificity for Study GE-012-101 was 70, 76, 81% for three different readers and 87% for Study GE-012-096. This data suggested that Visipaque CCTA can assist in the diagnostic evaluation of patients with suspected coronary artery disease.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The applicant has proposed dosing of Visipaque for the CCTA indication be based on their clinical experience, published literature [Bae K.T. Radiology Vol 256, 33-51, 2010], and the recommendations of professional organizations such as The Society of Cardiovascular Computed Tomography (SCCT) guidelines for performance of coronary computed tomographic angiography [Abbara et al. Journal of Cardiovascular Computed Tomography, Vol 3, 190-204, 2009] and The American College of Radiology (ACR). **Table 3.** summarizes these sources.

Table 3. Comparison of CCTA Contrast Dosing and Injection Parameters

Recommendation	GE-189-002	GE-012-096	[Bae 2010]	SCCT [Abbara et al. 2009]	ACR [ACR 2014]
Concentration mgI/mL	320	320	320-370	High	>300
Rate in seconds	4-5 mL	According to facility guidelines	4-5 mL	4-7 mL	>3-5 mL
Volume	70-80 mL	30-180 mL (mean 91.5 mL)	75-100 mL	Typically 50-120 mL	None
Criteria for the selection of contrast volume	Selected by the investigator	According to facility guidelines	Injection rate and scan duration	Injection rate and scan duration	Weight
Biphasic, Multiphasic or both?	Both	According to facility guidelines	Both	Both	Biphasic preferred
Recommended Iodine delivery rate (g I/s)	1.28-1.6	According to facility guidelines	1.28-1.6	None	None
Optimal attenuation in coronaries	Not measured	Not measured	300-350 HU	>250	None
Test bolus, bolus tracking or both?	Test bolus	According to facility guidelines	Both	Both	Both

No individualization of dose has been studied. The applicant recommends a dose of 1 ml/kg, not to exceed 150 mL, for patients >80 kg/mL. Both weight-based and fixed volume dosing have been used in published studies of CCTA [Nakaura et al. Investigative Radiology, 43, 512-519, 2008; Komatsu et al. Journal of Cardiology, 61, 155-161, 2013]. Nakaura et al. studied software-tailored contrast injections based on patient weight and compared them to a fixed-volume control group using 75 mL at 7.2 mL per second with no adjustments made for weight. Comparable image noise and quality were found between both groups. Nakaura et al. also compared patient weight-adjusted and fixed iodine protocols. Patients in both groups received contrast at a concentration of 370 mgI/mL. The fixed dose group received 80 mL at 4 mL/second (i.e., a constant injection duration of 20 seconds) while the weight-adjusted group received 1.0 mL/kg with injection rate adjusted to achieve an injection duration of 15 seconds. This study showed that, using qualitative scoring, beam hardening artifacts were higher in the fixed volume dose group but the level of enhancement in the coronaries was similar for both groups.

Reviewer's Dosing Recommendation

Both weight-based and fixed volume dosing have been used in published studies of CCTA. Nakaura et al. studied software-tailored contrast injections based on patient weight and compared them to a fixed-volume control group using 75 mL at 7.2 mL per second with no adjustments made for weight. Comparable image noise and quality were found between both groups. Nakaura et al. also compared patient weight-adjusted and fixed iodine protocols. Patients in both groups received contrast at a concentration of 370 mgI/mL. The fixed dose group received 80 mL at 4 mL/second (i.e., a constant injection duration of 20 seconds) while the weight-adjusted group received 1.0 mL/kg with injection rate adjusted to achieve an injection duration of 15 seconds. This study showed that, using qualitative scoring, beam hardening artifacts were higher in the fixed volume dose group but the level of enhancement in the coronaries was similar for both groups.

Bae advocates adjusting contrast dose (using iodine delivery rate) according to patient weight (as a surrogate for blood volume) with a trend towards a total recommended volume of iodinated contrast between 75 and 100 mL to achieve recommended opacification with fast multi-detector CT in an average sized adult. The Bae paper suggests, for modern fast CT scanners, this is best accomplished by increasing the iodine delivery rate with weight (either by increasing the iodine concentration at a fixed delivery volume and rate or by increasing the injection rate and total contrast volume) in order to maintain the same injection duration. Simply increasing the volume of contrast by patient weight above 70 kg at fixed concentration and injection rate would only serve to increase injection duration, which would be of no benefit to patients scanned on modern 64-slice CT scanners with CCTA acquisition times of 10 seconds or less.

The SCCT guidelines [Abbara et al. 2009] do not recommend adjustment of total contrast volume based on patient weight but only as a function of the injection rate and the injection duration to achieve a high intra-arterial opacification of more than 250 HU with an injection rate of 4-7 mL per second.

Based on these sources taken together, we agree with the applicant's proposed dosing recommendations, with the exception that we recommend that an option for weight-based dosing – for all patients, not only patients of large body weight – be added to the applicant's dosing table. The dosing table of the current FDA proposed package insert is reproduced, below (**Table 4**).

Table 4. Recommended Dosing for CCTA

ADULTS and PEDIATRIC PATIENTS[1] 12 YEARS OF AGE AND OLDER **VISIPAQUE (320 mg Iodine/mL) DOSING RECOMMENDATIONS FOR CCTA**						
Procedure	**Main VISIPAQUE Volume[2]**	**VISIPAQUE /saline Dilution Volume**	**Saline Flush**	**Injection Rate**	**Minimum VISIPAQUE Volume**	**Maximum VISIPAQUE Volume**
Without Dilution	70-80 mL[3,4]		40-50 mL	4-7 mL/sec	50 mL	150 mL
With Dilution	50-60 mL[4]	50 mL diluted VISIPAQUE (20 mL VISIPAQUE plus 30 mL saline)	20 mL	4-7 mL/sec	80 mL	225 mL

[1]For pediatric patients aged 12-17, recommended dose is 1-2 mL/kg.
[2]The main VISIPAQUE volume may be preceded by a test bolus consisting of 20 mL VISIPAQUE, immediately followed by a 20 mL saline flush, both injected at rate of 4-7 mL/sec.
[3]Alternatively, a dose of 1 mL/kg may be used to calculate total VISIPAQUE dose (excluding any test bolus).
[4]For CCTA acquired at < 120 kVp, the dose of VISIPAQUE may be reduced by up to 15% in patients < 85 kg and BMI < 30 kg/m^2. For CCTA acquired on a scanner with more than 64 detector rows, the dose of VISIPAQUE may be reduced in proportion to the scan duration.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

For routine CCTA procedures (i.e. patients weighing ≤80 kg with scans acquired at 120 kVp on 64-slice scanners) using Visipaque 320 mgI/ mL, is the applicant proposes (b) (4) . This should result in peak opacification of >300 HU in the coronary arteries and adequate to excellent contrast-to-noise ratio.

When performing CCTA in patients >80kg, image noise levels typically are higher. Increasing arterial opacification levels can maintain an adequate contrast-to-noise ratio to allow for adequate coronary lumen visualization. Therefore, the dose for patients > 80 kg should be 1 mL/kg up to a maximum of 150 mL, including any test bolus.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Visipaque Injection is administered intravenously– food-drug interactions are not expected. No drug-interaction studies were conducted to support the new indication. This is acceptable, as the new indication does not introduce any new concern regarding drug interactions.

4. APPENDICIES

4.1 Appendix 1: Applicant's annotated proposed package insert

4.2 Appendix 2: FDA's currently recommended package insert version

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/s/

CHRISTY S JOHN
03/15/2017

GENE M WILLIAMS
03/15/2017
I concur with the recommendations