DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Norma Vanderhorst
Labeling Specialist
GE Healthcare
101 Carnegie Center
Princeton, NJ 08540

RE: NDA #20-351, 20-808
Visipaque™ (iodixanol) Injection
MACMIS #18176

Dear Ms. Vanderhorst:

As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed GE Healthcare's (GE) website (http://md.gehealthcare.com/visipaque) for its drug product, Visipaque™ (iodixanol) Injection (Visipaque).[1] The website is misleading because it presents unsubstantiated comparative claims and omits and minimizes the risks associated with Visipaque. Thus, the website misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & (n); 321(n), and FDA's implementing regulations. See 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i); (e)(7)(i) & (viii). Furthermore, GE failed to submit a copy of the website accompanied by a completed transmittal Form FDA-2253 at the time of its initial publication, as required by 21 CFR 314.81(b)(3)(i).

Background

According to its FDA-approved product labeling (PI), Visipaque is indicated for the following (emphasis in original; footnotes omitted):

> **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 angiography), peripheral arteriography, visceral arteriography, and cerebral arteriography.

[1] Visipaque webpage, at http://md.gehealthcare.com/visipaque (last accessed January 7, 2010).

> **INTRAVENOUS**
> VISIPAQUE Injection (270 mgI/mL) is indicated for CECT [contrast-enhanced computed tomography] 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.

The Clinical Trials section of the PI states that the efficacy assessment of Visipaque was based on quality of the radiographic diagnostic visualization (i.e., either excellent, good, poor, or none) and on the ability to make a diagnosis (i.e., either confirmed a previous diagnosis, found normal, or diagnosed new findings). Patients treated with Visipaque were compared to those receiving active controls (ioxaglate, iohexol, iopromide, and meglumine-sodium diatrizoate) at concentrations which were similar to those of Visipaque. The clinical trials evaluated intra-arterial administration (angiocardiography, cerebral arteriography, peripheral arteriography, and visceral arteriography) and intravenous administration (excretory urography, CECT of the head and body, and peripheral venography). The results of Visipaque-treated patients were similar to those of the active controls.

Visipaque has a boxed warning which states, "**NOT FOR INTRATHECAL USE**" (emphasis in original), which is further emphasized and elaborated on in the Contraindications section of the PI and in the following bolded warning (emphasis in original):

> **WARNINGS**
> **SERIOUS ADVERSE EVENTS—INADVERTENT INTRATHECAL ADMINISTRATION**
> Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not administered intrathecally.

In the pediatric population, Visipaque is contraindicated in those who have undergone prolonged fasting and in patients who have been administered a laxative before drug injection. Visipaque is also associated with other serious risks. The PI includes warnings regarding inhibition of blood coagulation; serious, rarely fatal, thromboembolic events which therefore necessitate meticulous intravascular administration technique, particularly during angiographic procedures, to minimize thromboembolic events; use in patients with severely impaired renal function, combined renal and hepatic disease, combined renal and cardiac disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered; use in patients with multiple myeloma or other paraproteinaceous diseases; reports of thyroid storm following the intravascular use of iodinated radiopaque contrast agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule; use in patients with known or suspected pheochromocytoma; and promotion of sickling in individuals who are homozygous for sickle cell disease.

Additionally, the PI contains precautions regarding the dangers of preparatory dehydration, which may contribute to acute renal failure in patients with advanced vascular disease, congestive heart disease, diabetic patients, and other patients such as those on medications

which alter renal function and the elderly with age-related renal impairment; serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions; and potential delayed hemodynamic renal function disturbances in patients with congestive heart failure receiving concurrent diuretic therapy.

Furthermore, the Adverse Events section of the PI states the following (in pertinent part):

> As with other contrast agents, VISIPAQUE is often associated with sensations of discomfort, warmth or pain. In a subgroup of 1259 patients, for whom data are available; similar percentages of patients (30%) who received VISIPAQUE or a comparator had application site discomfort, pain, warmth or cold. VISIPAQUE had a trend toward fewer patient reports of moderate or severe pain or warmth; however, whether or not this related to the dose, rate of administration, site of injection or concentration has not been determined.

Unsubstantiated Comparative Claims

The website includes the following claims:

- "At all iodine concentrations, [Visipaque] is the only isosmolar contrast medium available for intravascular use."
- "Patient-procedure friendly, particularly when risk is high"[2]
- "With an osmolality equal to that of blood, VISIPAQUE was designed for patient safety and comfort. VISIPAQUE is also the only contrast medium formulated with sodium and calcium in a ratio equivalent to blood."
- "[Visipaque is f]ormulated with sodium and calcium at biologic levels."[3]
- "With an excellent safety profile, VISIPAQUE is approved for a broad range of diagnostic procedures…."

These claims misleadingly suggest that Visipaque offers a safety benefit compared to other products due to its unique formulation. In particular, the presentations indicate that Visipaque has superior patient safety and comfort characteristics because it is isosmolar to blood/formulated with sodium and calcium in a ratio equivalent to blood. However, we are not aware of substantial evidence or substantial clinical experience to support the implication created by these claims that patients will be safer or more comfortable if they use Visipaque instead of other contrast media. As indicated in the Clinical Trials section of the PI, Visipaque was only <u>comparable</u> in efficacy and safety to other ionic and nonionic imaging agents studied.

Furthermore, the implication that Visipaque is safer than other contrast media in high risk patients ("Patient-procedure friendly, particularly when risk is high") is not supported by substantial evidence or substantial clinical experience. The Davidson, et al. reference that is cited to support this claim only states that angiographic and procedural complications "<u>tended</u> to be less frequent" (emphasis added) for the Visipaque group compared with the other contrast agent group (ioxaglate) (17.3% versus 22%, respectively (**P=0.093, a non-**

[2] Davidson CJ, Laskey WK, Hermiller JB, et al. Randomized trial of contrast media utilization in high risk PTCA: The COURT Trial. *Circulation*. 2000;101:2172-2177.
[3] VISIPAQUE Prescribing Information.

significant finding)). Thus, this reference does not constitute substantial evidence to support the implication that Visipaque is safer than other alternatives for high-risk patients.

Similarly, the website includes the following claims regarding Visipaque's efficacy:

- "[Visipaque p]rovides excellent diagnostic efficacy."[4,5]
- "[Visipaque h]elps improve efficiency, and maximize[s] contrast for high-quality images and diagnostic outcomes."[6]

These claims misleadingly suggest that Visipaque offers excellent images and results in better diagnostic outcome compared to other products, when this has not been demonstrated by substantial evidence or substantial clinical experience. The references cited in support of these claims do not support the implication that use of Visipaque (versus other contrast media) will offer "excellent" images and the greatest possible diagnostic outcome. Specifically, the Klow, et al. reference had readers classify films as "nondiagnostic, suboptimal, or optimal" regarding diagnostic information and radiographic efficacy; "excellent" was not a specified category. Although the other two references (Hill, et al., and Spencer, et al.) state that the image quality and diagnostic efficacy of patients treated with Visipaque were good or excellent, the image quality and diagnostic efficacy of patients treated with other contrast agents were similar, or equivalent. In addition, the Spencer, et al. reference did not evaluate the efficiency of Visipaque. Thus, there was no significant difference in image quality among the contrast agents studied. Furthermore, the Clinical Trials section of the Visipaque PI states, "Visualization ratings were good or excellent in 100% of patients given VISIPAQUE . . . . The results were similar to those of the active controls [ioxaglate, iohexol, iopromide, and meglumine-sodium diatrizoate]" (emphasis added). Thus, we are not aware of support for the implication that Visipaque offers excellent visualization that results in better diagnostic outcomes than other products.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The website presents numerous safety and efficacy claims for Visipaque, but omits important information from the drug's bolded warning regarding serious adverse events reported due to inadvertent intrathecal administration, in addition to other important risk information discussed in the Background section above.

The only risk information included on the website are general statements concerning the risks of blood coagulation, clotting, thromboembolic events, and cautious use in certain disease states. Important information from the PI regarding, for example, the potential for serious, life-threatening, fatal anaphylactoid or cardiovascular reactions are not disclosed. As such,

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[4] Klow NE, Levorstad K, Berg KJ, et al. Iodixanol in cardioangiography in patients with coronary artery disease. Tolerability, cardiac and renal effects. *Acta Radiol*. 1993;34:72-77.
[5] Hill JA, Cohen MB, Kou WH, et al. Iodixanol, a new isosmotic nonionic contrast agent compared to iohexol in cardiac angiography. *Am J Cardiol*. 1994;74:57-63.
[6] Spencer CM, Goa KL. Iodixanol: a review of its pharmacodynamic and pharmacokinetic properties and diagnostic use as an X-ray contrast medium. *Drugs*. 1996;52:899-927.

the overall effect of these presentations minimizes the risks associated with Visipaque and misleadingly suggests that the drug is safer than has been demonstrated. We note a link to the Visipaque PI on the left-hand side of the website; however, this link does not mitigate the misleading omission of the risks associated with Visipaque.

Furthermore, the claims cited in the previous section, which explicitly and implicitly suggest that Visipaque has an "excellent safety profile," serve to further minimize the risks associated with Visipaque. As stated above in the Background section, Visipaque has a boxed warning, bolded warning, and numerous contraindications, warnings, precautions, and adverse events associated with its use.

The presentation and placement of the risk information that is included for Visipaque on the webpage further minimizes the serious risks associated with the drug. Unlike the sections marked with bolded headers such as, "Product Highlights" and "Product Description," the risk information does not have any signal to indicate that this is important safety information for the reader. In addition, the risk information is placed at the very bottom of the webpage after the reference list. The totality of these factors minimizes the risk information relative to the other information presented on the webpage.

Failure to Submit on Form FDA-2253

FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. GE did not submit a copy of the website referred to in this letter to DDMAC under cover of Form FDA-2253 at the time of its initial publication as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the website misbrands Visipaque in violation of the Act, 21 U.S.C. 352(a) & (n); 321(n), and FDA's implementing regulations. See 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i); (e)(7)(i) & (viii). Furthermore, GE failed to submit the website to FDA under cover of Form FDA-2253 at the time of its initial publication, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that GE immediately cease the dissemination of violative promotional materials for Visipaque, such as those described above. Please submit a written response to this letter on or before January 22, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Visipaque that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to

MACMIS #18176 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Visipaque comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michelle Safarik, MSPAS, PA-C
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20351	ORIG-1	GE HEALTHCARE	VISIPAQUE 270
NDA-20808	ORIG-1	GE HEALTHCARE	VISIPAQUE 270

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/s/

MICHELLE L SAFARIK
01/07/2010