



VISIPAQUE™ (IODIXANOL) INJECTION

WARNING: NOT FOR INTRATHECAL USE
Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

Important safety information and references may be found at the bottom of this page



How a swim in the sea led to the evolution of contrast media

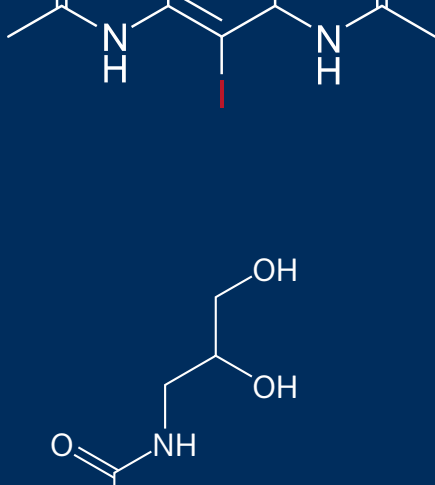
1960s

Inspired by a swim in the sea, the Swedish radiologist Torsten Almén set out to reduce the osmolality of iodinated contrast media (CM), championing the evolution **from high-osmolar CM (HOCM)...**

Osmolality describes the concentration of solute/kg of water¹

Diatrizoate

- Osmolality: 1940-2140 mOsm/kg H₂O²
- Iodine atoms/particles in solution: 3/1²

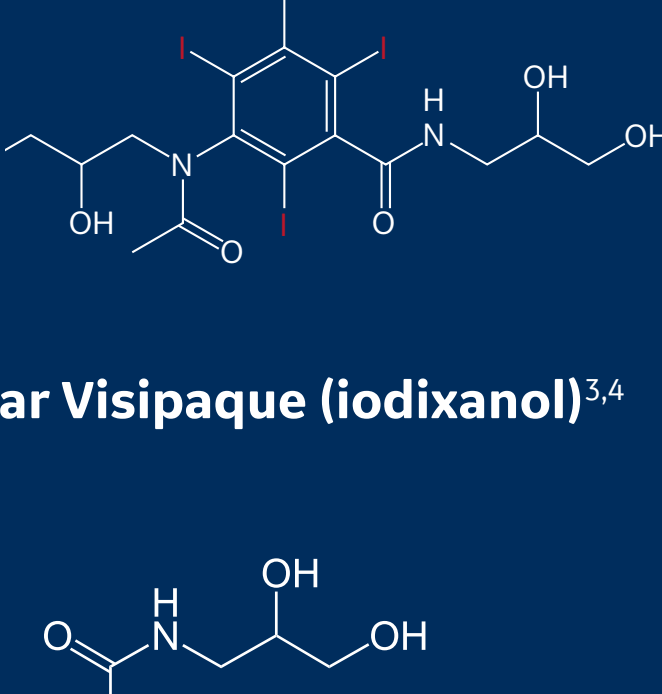


1980s

... to low-osmolar CM (LOCM)...

Iohexol

- Osmolality: 640-780 mOsm/kg H₂O²
- Iodine atoms/particles in solution: 3/1²

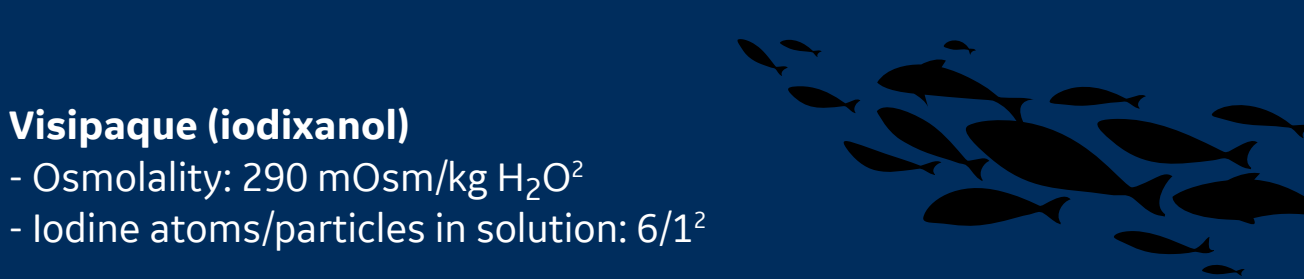


1993

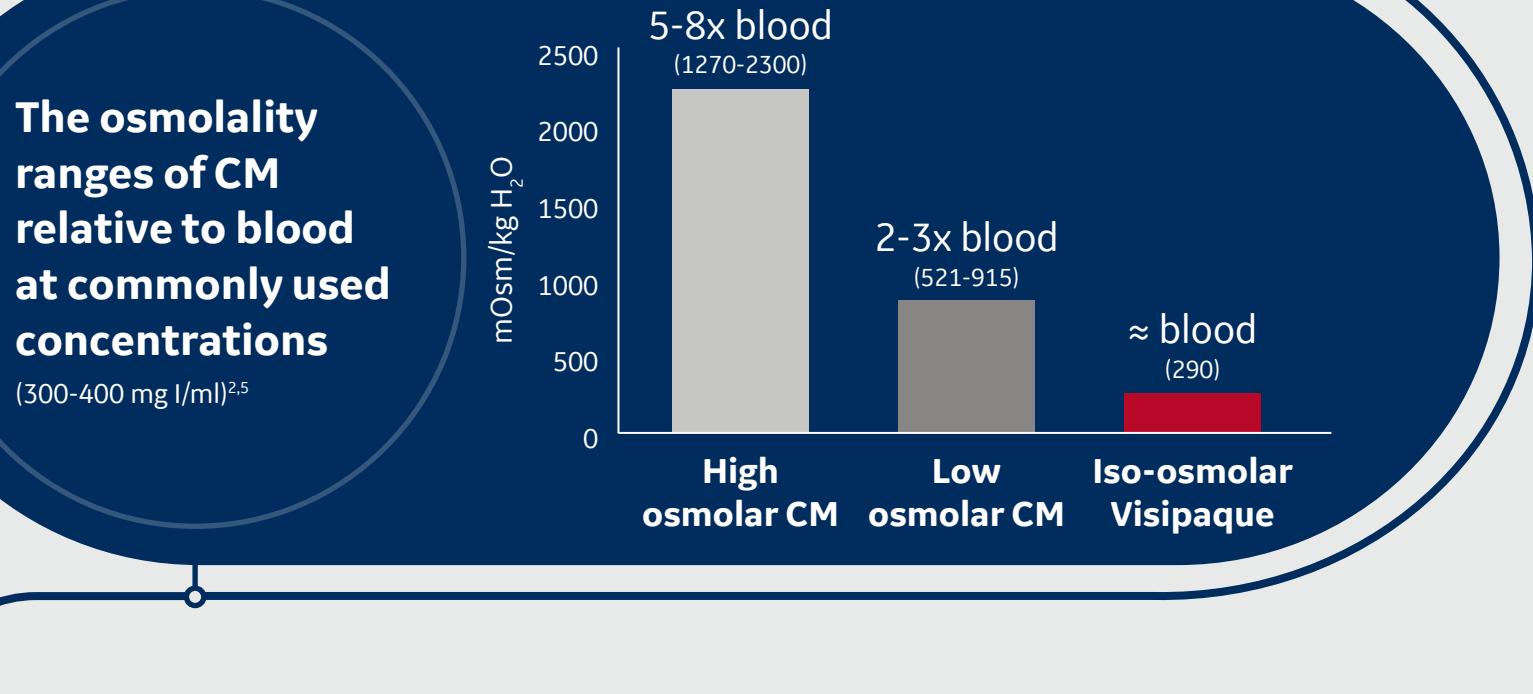
... and ultimately, to iso-osmolar Visipaque (iodixanol)^{3,4}

Visipaque (iodixanol)

- Osmolality: 290 mOsm/kg H₂O²
- Iodine atoms/particles in solution: 6/1²



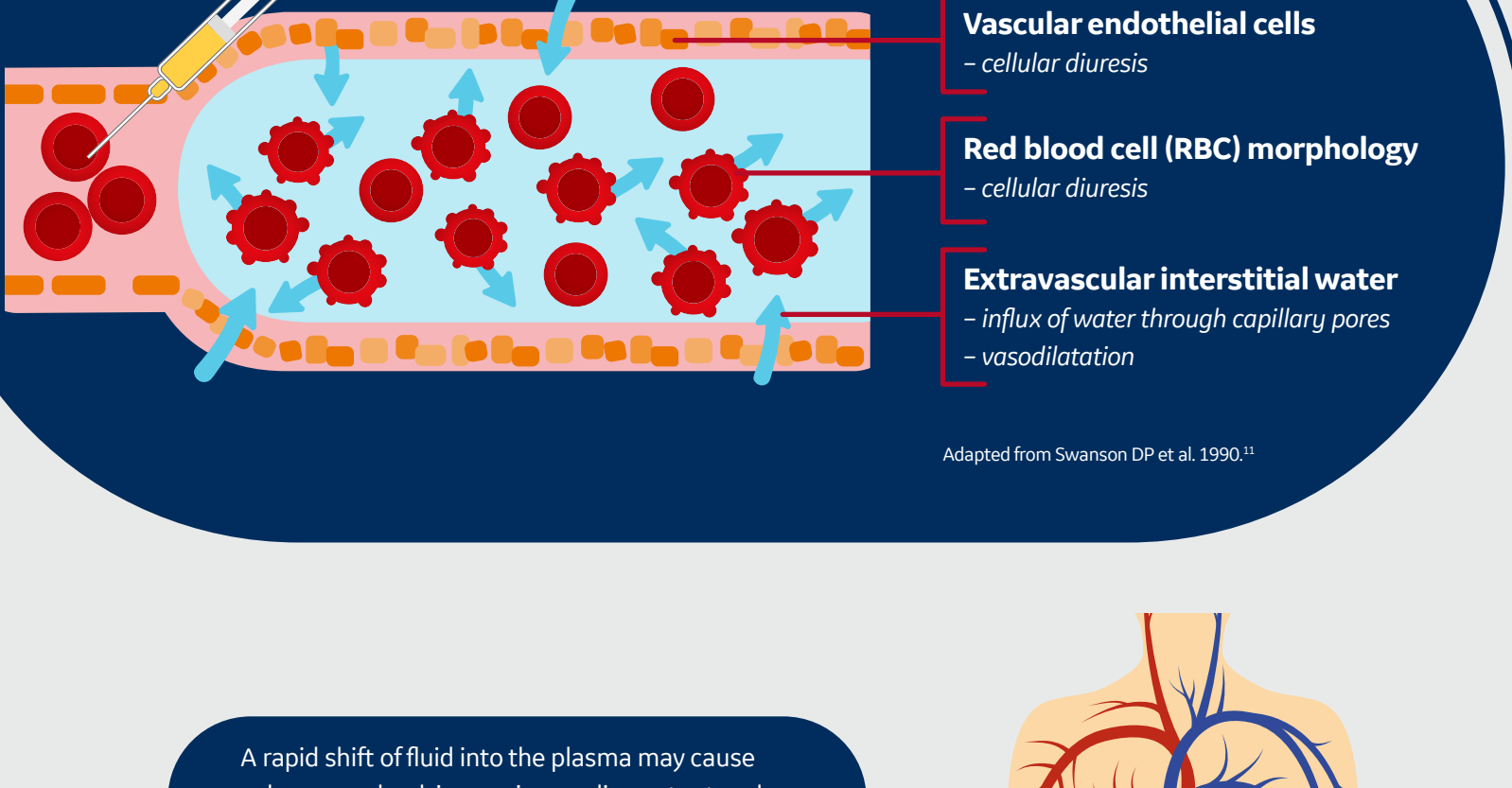
Visipaque is iso-osmolar to blood at all concentrations⁵



The osmolality ranges of CM at commonly used concentrations
(300-400 mg I/ml)^{2,5}

The osmolality of a CM may be associated with its cardiac and renal tolerability, as well as its impact on patient comfort⁶⁻¹⁰

Injection of hyperosmolar CM may induce a number of vascular changes¹¹

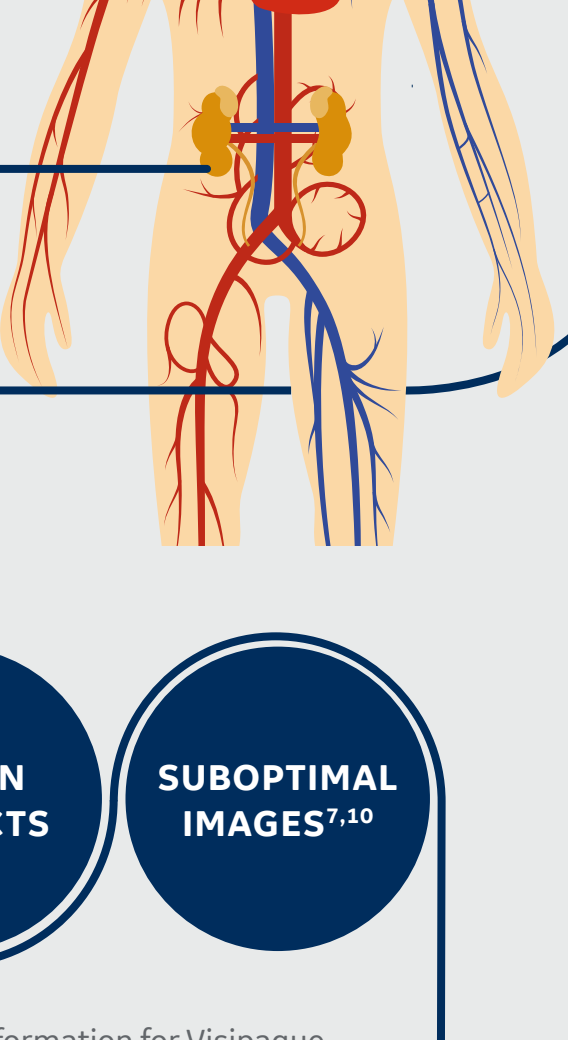


Adapted from Swanson DP et al. 1990.¹¹

A rapid shift of fluid into the plasma may cause volume overload, increasing cardiac output and ventricular end-diastolic/arterial pressures¹¹

Adverse changes in RBC morphology may affect capillary perfusion and impair the microcirculation of vital organs such as the kidneys^{7,8}

Vasodilation and adverse changes in blood and endothelial cells may cause sensations of discomfort such as flushing, pain, and warmth⁷



Formulated for patient comfort, Visipaque represents the evolution of iodinated CM towards:^{15,17,18}

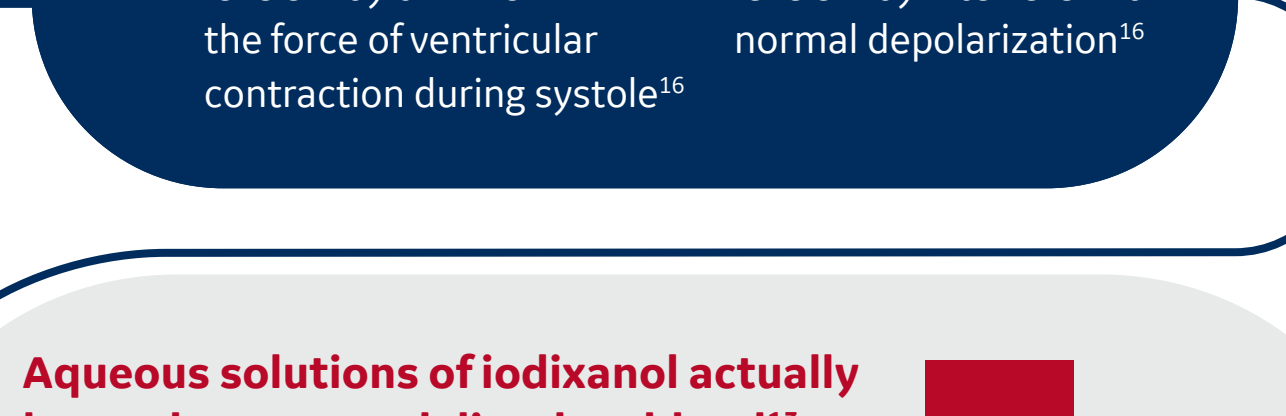
Iso-osmolality...

... and isotonicity

Visipaque is made iso-osmolar and isotonic¹² with the addition of key electrolytes¹³

Isotonic solutions have equal concentrations of impermeable solutes on either side of a membrane¹⁴

CM effects on myocytes, such as the myocardium, may be due to the imbalance between intracellular and extracellular electrolytes as the agent circulates¹⁵



Aqueous solutions of iodixanol have a lower osmolality than blood¹³

This osmolality gap is filled by the addition of sodium and calcium, resulting in an isotonic solution with a sodium/calcium ratio equivalent to blood^{12,13}



References:

- Speck U. Physicochemical properties of water-soluble contrast media. In: X-Ray Contrast Media. Overview, use and pharmaceutical aspects. Springer, Berlin 2018.
- Jakobsen JA. Physiological effects of contrast media for use in multidetector row computed tomography. *Eur J Radiol.* 2007;62(Suppl.):S14-S25.
- Nyman U, Ekberg O, Aspelin P, Torsten Almén (1931-2016): the father of non-ionic iodine contrast media. *Acta Radiol.* 2016;57(9):1072-1078.
- Pollack HM. History of Iodinated Contrast Media. In: Thomsen HS, Muller RN, Mattrey RF (eds). Trends in Contrast Media. Springer-Verlag, Berlin 1999.
- Davidson C, Stacul F, McCullough PA, et al. Contrast medium use. *Am J Cardiol.* 2006;98(6A):42K-58K.
- 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(6):899-927.
- Kerl JM, Nguyen SA, Lazarchick J, et al. Iodinated contrast media: effect of osmolality and injection temperature on erythrocyte morphology in vitro. *Acta Radiol.* 2008;49(3):337-343.
- Katsanos K, Moutzouri A, Karnabatidis D, Siablis D, Athanassiou G. Influence of contrast media on red blood cell deformability. *Clin Hematol Microcirc.* 2008;39(1-4):87-91.
- McCullough PA, Choi JP, Feghali GA, et al. Contrast-induced acute kidney injury. *J Am Coll Cardiol.* 2016;68(13):1465-1473.
- McCullough PA, Capasso P. Patient discomfort associated with the use of intra-arterial iodinated contrast media: a meta-analysis of comparative randomized controlled trials. *BMC Med Imaging.* 2011;11:12.
- Swanson DP, Chilton HM, Thrall JH. In: Pharmaceuticals in Medical Imaging. Collier MacMillan Publishers, London 1990.
- Visipaque Prescribing Information. Marlborough, MA: GE Healthcare; 2022.
- Eivindik K, Sjøgren CE. Physicochemical properties of iodixanol. *Acta Radiologica.* 1995;36(Suppl.399):32-38.
- Stittell W. Membrane isolation methods. In: An Introduction to Biological Membranes. Elsevier Science, 2016.
- Pedersen HK. Electrolyte addition to nonionic contrast media - cardiac effects during experimental coronary arteriography. *Acta Radiol Suppl.* 1996;37(Suppl.405):1-31.
- Chai C-M, Almén T, Bååth L, Besjakov J. Adding sodium and calcium ions to the contrast medium iodixanol reduced the risk of ventricular fibrillation during perfusion of the left coronary artery in pigs: effects of electrolytes, viscosity, and chemotoxicity of an isotonic perfusate. *Acad Radiol.* 2004;11(5):583-593.
- Almén T. Visipaque - a step forward: a historical review. *Acta Radiol.* 2016;57(5):e47-e63.
- Fountainaine H, Harnish P, Andrew E, Grynne B. Safety, tolerance, and pharmacokinetics of iodixanol injection, a nonionic, isosmolar, hexa-iodinated contrast agent. *Acad Radiol.* 1996;3(Suppl.3):S475-S484.

CM, contrast media
HOCM, high-osmolar CM
LOCM, low-osmolar CM
RBC, red-blood cell

VISIPAQUE™ (IODIXANOL) INJECTION

PRODUCT INDICATIONS AND USE

Intra-Arterial Procedures
Adult and pediatric patients 12 years of age and older: Intra-arterial digital subtraction angiography (270 and 320 mg iodine/mL); angiocardiology (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography (320 mg iodine/mL). **Pediatric patients less than 12 years of age:** Angiocardiology, cerebral arteriography, and visceral arteriography (270 mg iodine/mL)

Intravenous Procedures
Adult and pediatric patients 12 years of age and older: Computed tomography (CT) imaging of the head and body (270 and 320 mg iodine/mL); excretory urography (270 and 320 mg iodine/mL); peripheral venography (270 mg iodine/mL); coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease (320 mg iodine/mL). **Pediatric patients less than 12 years of age:** CT imaging of the head and body (270 mg iodine/mL); excretory urography (270 mg iodine/mL)

IMPORTANT SAFETY INFORMATION ABOUT VISIPAQUE™ (IODIXANOL)

WARNING: NOT FOR INTRATHECAL USE
Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

CONTRAINDICATION:
Visipaque Injection is contraindicated for intrathecal use.

WARNINGS AND PRECAUTIONS:

- Hypersensitivity Reactions:** Life-threatening or fatal reactions can occur. Most severe reactions develop shortly after the start of the injection, but reactions can occur up to hours later. Always have emergency equipment and trained personnel available.
- Contrast Induced Acute Kidney Injury:** Acute injury including renal failure can occur. Minimize dose and maintain adequate hydration to minimize risk.
- Cardiovascular Reactions:** Life-threatening or fatal cardiovascular reactions, including hypotension, shock, and cardiac arrest have occurred with the use of Visipaque. Most deaths occur during injection or five to ten minutes later, with cardiovascular disease as the main aggravating factor. Use the lowest necessary dose of Visipaque in patients with congestive heart failure.
- Thromboembolic Events:** Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke can occur during angiocardiology procedures with both ionic and nonionic contrast agents.
- Extravasation and Injection Site Reactions:** Extravasation of Visipaque and extravasation of iodinated contrast media with severe arterial or venous disease. Ensure intravascular placement of catheters prior to injection.
- Thyroid Storm in Patients With Hyperthyroidism:** Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule.

- Hypertensive Crisis in Patients With Pheochromocytoma:** Hypertensive crisis has occurred after the use of iodinated contrast agents in patients with pheochromocytoma. Inject the minimum amount of contrast necessary, assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.

- Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age:** Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media. Among patients 0 to 3 years of age exposed to iodinated contrast media, thyroid dysfunction has been reported in 1% to 15% depending on the age of the patient and the dose of the iodinated contrast agent. Monitor these patients for thyroid function abnormalities and treat as clinically needed.

- Sickle Cell Crisis in Patients With Sickle Cell Disease:** Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease.
- Severe Cutaneous Adverse Reactions:** Severe cutaneous adverse reactions (SCARs) may develop from one hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS). Avoid administering Visipaque to patients with a history of a SCAR to Visipaque.

- Pediatric Use:** Pediatric patients at high risk of adverse reactions during and after administration of contrast agents include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, chronic heart failure, or a serum creatinine >1.5 mg/dL. Electrolyte addition to nonionic contrast agents may be at increased risk due to prolonged elimination of iodinated contrast agents.
- Geriatric Use:** While no overall differences in safety or effectiveness were observed in patients >65 years, greater sensitivity regarding some older individuals cannot be ruled out.

ADVERSE REACTIONS:

- Serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast agents, including Visipaque Injection.
- Most common adverse reactions (incidence greater than 0.5%) in adult patients after Visipaque injection: Discomfort, warmth, pain; Cardiovascular: angina. Gastrointestinal: diarrhea, nausea, vomiting. Nervous System: agitation, anxiety, insomnia, nervousness, dizziness, headache, migraine, unusual skin sensations, sensory disturbance, fainting, sensation of spinning. Skin: itchy rash, severe itching, hives. Special Senses: Smell, taste, and vision alteration. Pediatric patients experienced similar adverse reactions.

Please see the full prescribing information [here](#), including **Boxed Warning** for additional important safety information.

To report **SUSPECTED ADVERSE REACTIONS**, contact **GE Healthcare at 800 654 0118 (option 2, then option 1), or the FDA at 800 FDA 1088 or www.fda.gov/medwatch.**

