OptiRAY®

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Optimized Safety,

Image Quality and Procedure Efficiency in Interventional Cardiology

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Optimized Safety,

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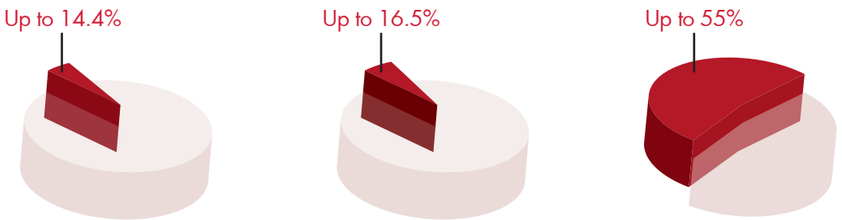
Frequent Occurrence of **Contrast-induced Nephropathy (CIN)**

CIN is a common and serious complication in patients undergoing coronary angiography or percutaneous coronary intervention (PCI) [1-6]

CIN incidence



Increased in-hospital complications and mortality [4-6]

Major adverse cardiac event (MACE)

15-fold increase vs. no CIN [4]

Persistent renal damage

21-fold increase vs. no CIN [5]

In-hospital mortality

5-fold increase vs. no CIN [6]

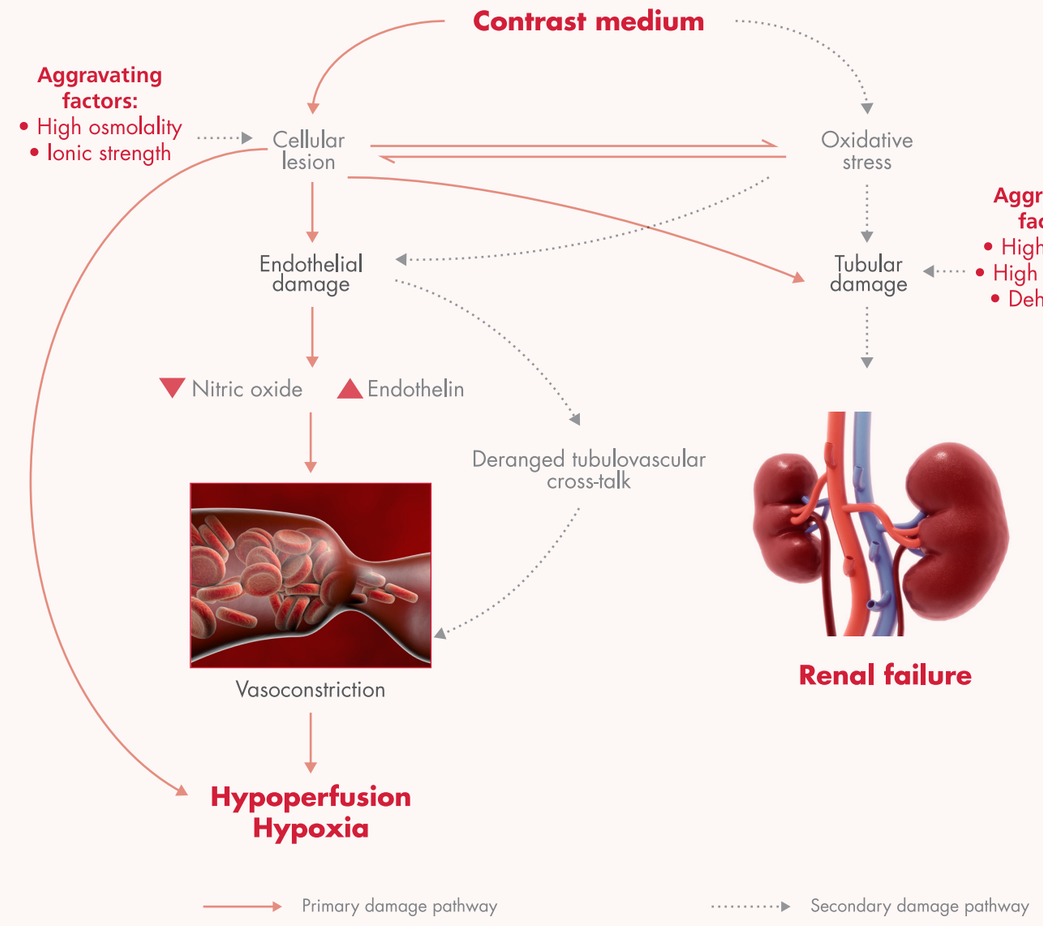
1-year mortality

4-fold increase vs. no CIN [6]

* Include patients with chronic kidney disease or diabetes.

Chemotoxic-type effects are related to physiochemical properties of contrast media, i.e. osmolality, viscosity, ionic strength [7,8]

Cellular and tissue damage caused by contrast media



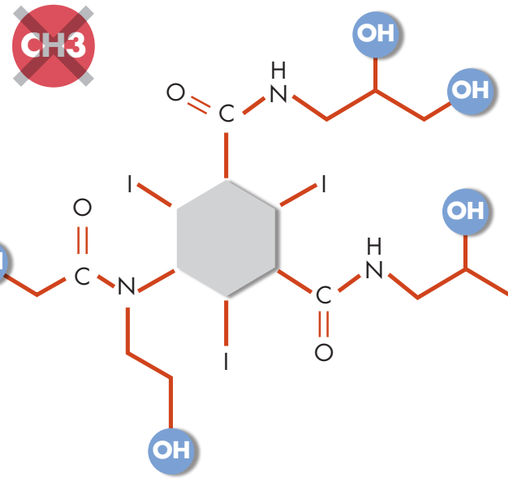
Adapted from Sendeski et al. 2011 [7]

References: **1.** Gami AS and Garovic VD. Contrast nephropathy after coronary angiography. Mayo Clin Proc. 2004;79:211-219. **2.** Rear R, et al. Heart. Contrast-induced nephropathy following angiography and cardiac interventions. 2016;102:638-648. **3.** Mehran R and Nikolsky E. Contrast-induced nephropathy: Definition, epidemiology, and patients at risk. Kidney Int Suppl. 2006;100:S11-S15. **4.** Bartholomew BA, et al. Am J Cardiol. Impact of Nephropathy After Percutaneous Coronary Intervention and a Method for Risk Stratification. 2004;93:1515-1519. **5.** Maioli M, et al. Circulation. Persistent Renal Damage After Contrast-Induced Acute Kidney Injury. 2012;125:3099-3107. **6.** Seeliger E, Eur Heart J. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. 2012;33:2007-2015. **7.** Sendeski MM. Pathophysiology of renal tissue damage by iodinated contrast media. Clin Exp Pharmacol Physiol. 2011;38:292-299. **8.**Thomsen HS. Management of acute adverse reactions to contrast media. In: Thomsen HS, editor. Contrast Media: Safety Issues and ESUR Guidelines. Heidelberg, Springer;2006. pp. 19-25.

OptiRAY® – Optimizing Your Interventional Cardiology Procedure

OptiRAY® contrast agent has six hydroxyl groups evenly arranged around the tri-iodinated benzene ring and has no methyl group. It is a non-ionic monomer that possesses properties of high hydrophilicity, low viscosity and low osmolality [9-11]

OptiRAY® chemical structure [9]



High hydrophilicity [11]

Lowers affinity to plasma proteins and cell membrane, thereby minimizing chemotoxicity [8]

Low osmolality [10]

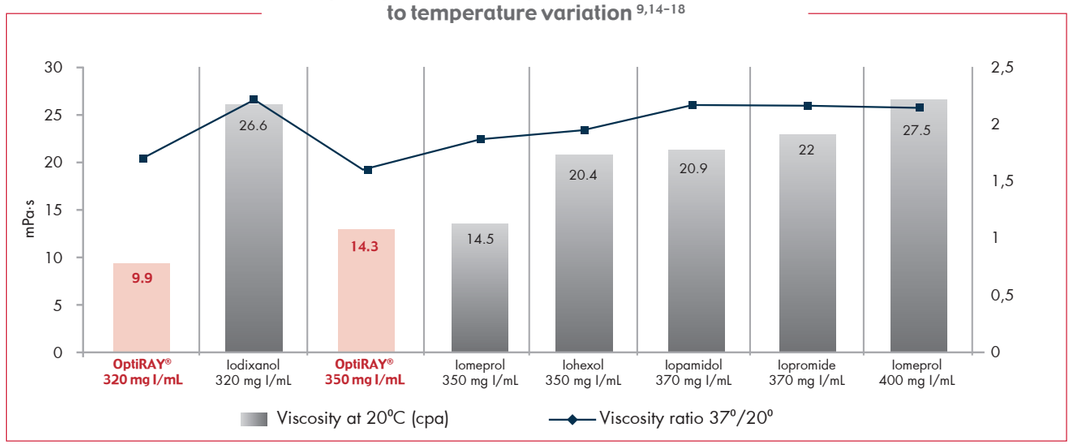
Hinders fluids shifting from the intracellular to extracellular space and thus hinders cell dehydration [8]

Potential benefits of low viscosity contrast agents

- May enable to reduce catheter size and sheath size, thus facilitating a minimally invasive approach and supporting the reduction of vascular and bleeding complications [10]
- Decreases clearance time vs. contrast agents with high viscosity [13]
- Enables high flow rate and low injection pressure that may improve opacification [10]
- Enables to reduce infusion time vs. fluids with high viscosity in same infusion conditions [12]

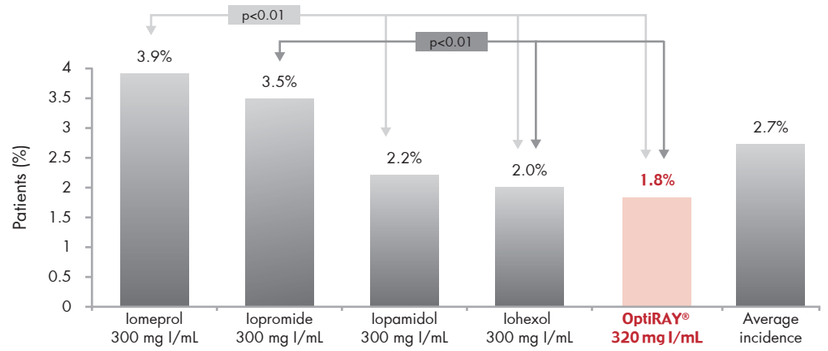
OptiRAY® 320 and **OptiRAY®** 350 have lower viscosity compared with iodixanol 320, iohexol 350, iopamidol 370, iopromide 370 and iomeprol 400 [9,14-18]

OptiRay®: low viscosity and low sensitiveness to temperature variation [9,14-18]



OptiRAY® 320 is among the tested contrast agents with lower incidence of acute adverse reactions, when compared to iomeprol 300 and iopromide 300 in the study by Gomi et al [19]

Incidence of acute adverse reactions



Adapted from Gomi et al. 2010 [19]

p<0.01 Iomeprol vs. iopamidol, iohexol or **OptiRAY®**

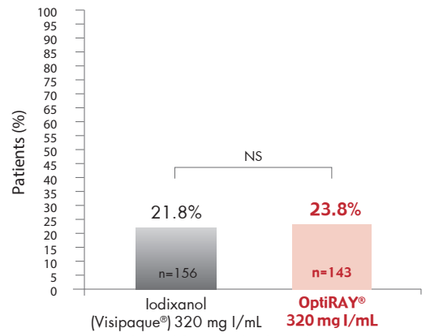
p<0.01 Iopromide vs. iohexol or **OptiRAY®**

References: **8.** Thomsen HS. Management of acute adverse reactions to contrast media. In: Thomsen HS, editor. Contrast Media: Safety Issues and ESUR Guidelines. Heidelberg, Springer;2006. pp. 19-25. **9. OptiRAY®** prescribing information. **10.** Voeltz MD, et al. The Important Properties of Contrast Media: Focus on Viscosity. J Invasive Cardiol. 2007;19:1A-9A. **11.** Le Mignon MM, et al. Preliminary European intravenous clinical experience with a new low osmolar, nonionic contrast medium: ioversol (Optiray). Eur J Radiol. 1991;13:126-133. **12.** Geenen RW, et al. Contrast-induced nephropathy: pharmacology, pathophysiology and prevention. Insights Imaging. 2013;4:811-820. **13.** Jost G, et al. The Impact of the Viscosity and Osmolality of Iodine Contrast Agents on Renal Elimination. Invest Radiol. 2010;45:255-261. **14.** Iodixanol prescribing information. **15.** Iohexol prescribing information. **16.** Iopromide prescribing information. **17.** Iopamidol prescribing information. **18.** Iomeprol prescribing information. **19.** Gomi T, et al. Are there any differences in acute adverse reactions among five low-osmolar non-ionic iodinated contrast media? Eur Radiol. 2010;20:1631-1635.

No Difference in Nephrotoxicity between Low-osmolar and Iso-osmolar Contrast Agents

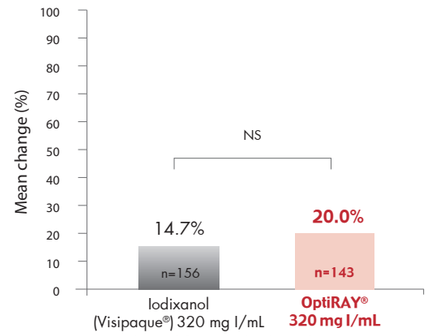
The nephrotoxicity of **OptiRAY®** 320 is not significantly different from that of iodixanol in patients with chronic kidney disease undergoing coronary angiography [20]

Incidence of CIN



Adapted from Rudnick et al. 2008 [20]

Mean peak percentage change of Scr from baseline

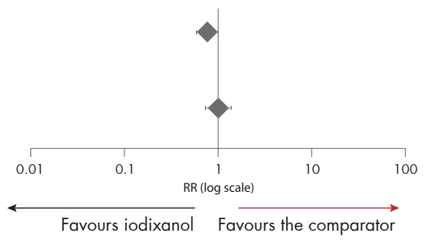


Adapted from Rudnick et al. 2008 [20]

In patients with intravascular contrast medium application, there is no significant difference in the relative risk of contrast-induced nephrotoxicity with iodixanol, compared with either low-osmolar contrast media [21]

Relative risk (RR) of CIN [21,*,†]

	RR (95% CI)
Iodixanol vs. low osmolar contrast media pooled together	0.80 (0.61-1.04)
Iodixanol vs. low osmolar contrast media other than iohexol	0.97 (0.72-1.32)



* An increase of at least 25% in serum creatinine level was used as definition for CIN when these data were available; otherwise, most closely related data given in publication were used.

† In the meta-analysis, only one study involved **OptiRAY®**, weighing 14.5% of the population in the comparison of iodixanol with low-osmolar contrast media pooled together and 19.5% in the comparison of iodixanol with low-osmolar contrast media other than iohexol.

▶ In a recent meta-analysis, iodixanol had a slightly and significantly lower CIN risk than low-osmolar contrast media, but the difference was not clinically significant. No significant difference in the risk of CIN was observed among various types of low-osmolar contrast media in the reviewed studies [22]

VALOR was a prospective double-blind trial comparing the nephrotoxicity of iodixanol (320 mg I/mL) with **OptiRAY®** (320 mg I/mL) in 337 patients with chronic kidney disease undergoing coronary angiography with or without PCI [20].

A meta-analysis of 25 randomized controlled clinical trials assessing serum creatinine levels before and after intravascular application of iodixanol or low-osmolar contrast media was conducted to compare the nephrotoxicity of iso-osmolar iodixanol with that of non-ionic low-osmolar contrast media. 3,270 patients were included in the meta-analysis [21].

Both low-osmolar and iso-osmolar contrast agents are recommended by international guidelines [23-29]

Scientific association	Recommendation for CIN prevention in at-risk patients	Type of contrast media	
		Low-osmolar	Iso-osmolar
Ref [23]	In patients with moderate to severe CKD, use of low-osmolar or iso-osmolar contrast media, with dose <350 mL or 4 mL/kg or total contrast volume/GFR<3.4 is associated with the highest COR (I) and LOE (A)*	√	√
Ref [24]	Use of iso-osmolar or low-osmolar iodinated contrast media, rather than high-osmolar iodinated contrast media, is recommended in patients at increased risk of CI-AKI (grade: I; LOE:B)†	√	√
Ref [25]	No difference in the rate of PC-AKI was observed between iodixanol and low osmolality agents after intravenous administration	√	√
Ref [26]	In patients with CKD undergoing angiography who are not undergoing chronic dialysis, either an iso-osmolar contrast medium (class: I, LOE: A)‡ or a low-molecular-weight contrast medium other than ioxaglate or iohexol is indicated (class I, LOE: B)¶	√	√
Ref [27]	Use of iso-osmolar or low-osmolar contrast media is recommended for patients with eGFR <45 mL/min for intravenous contrast media use or GFR <60 mL/min for intra-arterial contrast media studies	√	√
Ref [28]	The lowest possible volume of a low or iso-osmolar iodinated contrast media should be used in patients with risk factors for developing CI-AKI (not graded)	√	√
Ref [29]	Contrast media should be minimized, and either low-osmolar or iso-osmolar contrast media should be used in patients with CKD	√	√

* Class I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective; level A: data derived from multiple randomized clinical trials or meta-analyses.

† Level I: the recommendation can be evaluated as a candidate for developing a policy or a performance measure; grade B: moderate quality of evidence-the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

‡ Class I: procedure/treatment should be performed/administered; level A: data derived from multiple randomized clinical trials or meta-analyses.

¶ Class I: procedure/treatment should be performed/administered; level B: data derived from a single randomized trial or nonrandomized studies.

ACC = American College of Cardiology. ACR = American College of Radiology. AHA = American Heart Association. BCIS = British Cardiovascular and Intervention Society. CAR = Canadian Association of Radiologists. CKD = chronic kidney disease. CI-AKI = contrast-induced acute kidney injury. COR = class of recommendation. eGFR = estimated glomerular filtration rate. EACTS = European Association for Cardio-Thoracic Surgery. ESC = European Society of Cardiology. GFR = glomerular filtration rate. KDIGO = Kidney Disease Improving Global Outcomes. LOE = level of evidence. NS = not statistically significant (p≥0.05). PC-AKI = post-contrast acute kidney injury. RCR = The Royal College of Radiologists. SCAI = Society for Cardiovascular Angiography and Interventions. Scr = serum creatinine.

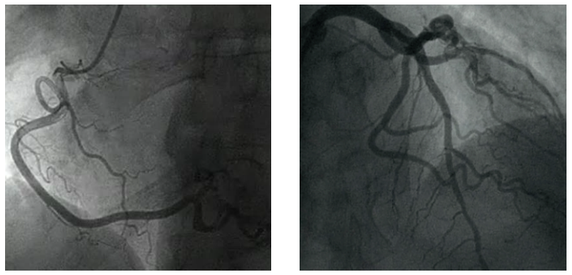
References: **20.** Rudnick MR, et al. Nephrotoxicity of iodixanol versus ioversol in patients with chronic kidney disease: The Visipaque Angiography/Interventions with Laboratory Outcomes in Renal Insufficiency (VALOR) Trial. Am Heart J. 2008;156:776-782. **21.** Heinrich MC, et al. Nephrotoxicity of Iso-osmolar Iodixanol Compared with Nonionic Low-osmolar Contrast Media: Meta-analysis of Randomized Controlled Trials. Radiology. 2009;250:68-86. **22.** Eng J, et al. Comparative Effect of Contrast Media Type on the Incidence of Contrast-Induced Nephropathy. Ann Intern Med. 2016;164:417-424. **23.** Windecker S, et al. 2014 ESC/EACTS Guidelines onmyocardial revascularization. Eur Heart J. 2014;35:2541-2619. **24.** Kidney Disease: Improving Global Outcomes. Kidney Inter Suppl. 2012;2:1-138. **25.** ACR Committee on Drugs and Contrast Media. ACR Manual on Contrast Media. Version 10.3. **26.** Kushner FG, et al. 2009 Focused Updates: STEMI and PCI Guidelines. Catheter Cardiovasc Interv. 2009;74:E25-E68. **27.** Owen RJ, et al. Canadian Association of Radiologists Consensus Guidelines for the Prevention of Contrast-Induced Nephropathy: Update 2012. Can Assoc Radiol J. 2014;65:96-105. **28.** Lewington A, et al. Prevention of contrast induced acute kidney injury (CI-AKI) in adults patients. Available at: www.renal.org/docs/default-source/guidelines-resources/joint-guidelines/Prevention_of_ContrastInduced_Acute_Kidney_Injury_CI-AKI_In_Adult_Patients.pdf (Accessed on 19 December 2016). **29.** Bashore TM, et al. 2012 American College of Cardiology Foundation/Society for Cardiovascular Angiography and Interventions Expert Consensus Document on Cardiac Catheterization Laboratory Standards Update. J Am Coll Cardiol. 2012;59:2221-2305.

OptiRAY® – High Diagnostic Image Quali ty for Cardiac Procedures

In a clinical study evaluating the efficacy of **OptiRAY®** 350 in patients undergoing selective coronary angiography with left ventriculography, 92.5% of procedures were rated as excellent or good in overall quality [30]

Coronary angiography

- Concentration: **OptiRAY®** 350 mg I/mL
- Volume: 340 mL
- Volume per injection: 14 mL
- Flow rate: 4 mL/s



Coronary angiograms in a 55-year-old male patient with in-stent coronary total occlusion (CTO)

Courtesy from www.incathlab.com
[Dr. Carlino M et al. (San Raffaele Scientific Institute, Italy)]

incathlab clinical cases with OptiRAY®

incathlab
THE INTERACTIVE CARDIOVASCULAR CHANNEL

- Complex CTO PCI in retrograde (failure) Milan, Italy, 2017
  https://www.incathlab.com/en/videos/1-coronary/68-cto/1508-complex-cto-pci-in-retrograde-failure
- CTO of mid RCA St. Gallen, Switzerland, 2017
  https://www.incathlab.com/en/videos/1-coronary/68-cto/1775-cto-of-mid-rca
- RCA with massive calcifications Barcelona, Spain, 2016
  https://www.incathlab.com/en/videos/1-coronary/71-pci/1459-rca-with-massive-calcifications

A multicenter, double-blind randomized study compared the efficacy of **OptiRAY®** 350 with iohexol 350 mg I/mL in 160 patients undergoing selective coronary arteriography with left ventriculography. Each coronary arteriography study was evaluated by the investigator to determine the quality of each examination by grading it as poor, fair, good or excellent; each study was also rated as diagnostic or non-diagnostic. All coronary arteriography procedures in both groups were rated as diagnostic by the investigators [30].

OptiRAY® has a broad range of indications in imaging procedures [9]

OptiRAY®	Indications [9]
OptiRAY® 350	■ Indicated in adults for angiography, including digital subtraction angiography (DSA), throughout the cardio vascular system. ■ Indicated for contrast enhanced computed tomographic imaging of the head and body, intravenous excretory urography, intravenous digital subtraction angiography and venography. ■ Indicated in children for angiocardiography.
OptiRAY® 320	■ Indicated in adults for angiography throughout the cardiovascular system. The uses include cerebral, coronary, peripheral, visceral and renal arteriography, venography, aortography, and left ventriculography. ■ Indicated for contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography. ■ Indicated in children for angiocardiography, contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography.
OptiRAY® 300	■ Indicated for cerebral angiography and peripheral arteriography. ■ Indicated for contrast enhanced computed tomographic imaging of the head and body, venography, and intravenous excretory urography.

Not all the presentations and indications may be available in your country.
Please check with your local Guerbet representative for more information.

References: **9. OptiRAY®** prescribing information. **30.** McGaughey MD, et al. A double-blind study comparing the safety, tolerability, and efficacy of ioversol-350 and iohexol-350 in coronary arteriography with left ventriculography. J Invasive Cardiol. 1991;3:272-277.

Bring the Benefits of OptiRAY® to Your Cath Lab Practice

OptiRAY® contrast agent is available in vials and pre-filled syringes, which can now be coupled with our injector Illumena® Néo and its disposables to provide an integrated solution for cardiac imaging

Why choose this combination of products CATH LAB practice?

- An easy-to-use and newly updated contrast delivery system perfectly suited to contrast medium with relevant physicochemical properties to upgrade your cath lab routine
- The best-in-class safety profile combined to a high image quality to optimize your interventional cardiology procedure
- A combination that will simplify your daily work

The combination that makes the difference in your Cath Lab

OTHER SOLUTIONS FOR YOUR CATH LAB PRACTICE

[Opti**RAY®** in pre-filled syringes + Illumena® Neo + disposables by LF]

Our simple, functional and reliable injector can also be used with our ready-to-use presentation

Opti**RAY®** in pre-filled syringes supplied in 3 different concentrations:
300, 320 and 350 mg I/mL
Available from 50 to 125 mL volumes

The Illumena® Néo is a medical device (Class: II b, CE0123) intended for use by medical imaging and diagnostic health professionals, for injecting radiopaque contrast media into a patient's vascular system during CT examinations, Coronary Angiography, Cardiac Catheterisation or Interventional procedures.
For complete information about precautions and optimal usage, we recommend consulting the instruction for use / user's manual.
Illumena® Néo Notified Body: TUV SUD Product Service GmbH.
Manufacturer: Liebel-Flarsheim Company LLC, 2111 East Galbraith Road, Cincinnati, OH 45237, USA.

CATH LAB = catheterization laboratory.

Please check with local representative for the volume, concentration and availability in your country.
A designated pre-filled faceplate is required in order to use **OptiRAY®** pre-filled syringe with Illumena® Neo.

Please contact our local representative for more information about our injectors and disposables

www.guerbet.com

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Prescribing information: Please refer to the Summary of Product Characteristics before prescribing. **Composition:** OPTIRAY® 240 loversol, 509 mg/ml, which is equivalent to 240 mg/ml of elemental iodine. OPTIRAY® 300 loversol, 636 mg/ml, which is equivalent to 300 mg/ml of elemental iodine. OPTIRAY® 320 loversol, 678 mg/ml, which is equivalent to 320 mg/ml of elemental iodine. OPTIRAY® 350 loversol, 741 mg/ml, which is equivalent to 350 mg/ml of elemental iodine. **Indications:** OPTIRAY® non-ionic X-ray contrast medium for injection or infusion. Depending on the preparation, it is indicated for use in cerebral, coronary, peripheral, visceral and renal angiography, in aortography, left ventriculography, venography, intravenous excretory urography and computed tomography (CT) of the head and body. Except for OPTIRAY® 300, safety and effectiveness of OPTIRAY® in children has not yet been established. **Posology and Method of Administration:** The dosage may vary between 1 ml and 150 ml, maximum total dose 250 ml or less. Please refer to the Summary of Product Characteristics for the recommended dosage schedule. **Contraindications:** Proven hypersensitivity to iodine-containing contrast media. Manifest hyperthyroidism. **Special Warnings and Precautions for Use:** As with all other X-ray contrast media, OPTIRAY® may cause anaphylaxis or other manifestations of pseudo-allergic intolerance reactions, e.g. nausea, vomiting, dyspnoea, erythema, urticaria and hypotension. Pretesting cannot be relied upon to predict severe reactions. The thorough assessment of the medical history of the specific patient may be more accurate in predicting potential adverse reactions. A positive history of allergy is not a contraindication, but does require caution. Diagnostic procedures, which involve the use of iodinated intravascular contrast agents, should be performed under the direction of personnel skilled and experienced in the particular procedure to be performed. Serious or fatal reactions have been associated with the administration of iodinated X-ray contrast media. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognising and treating adverse reactions of all types should always be available for at least 30 to 60 minutes after administration. Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed haemodynamic disturbances, which may be associated with a transitory increase in the circulating osmotic load. All other patients should be observed for at least one hour after the application, as it has been reported that most of the adverse events occur in this period. The patient should also be informed that allergic reactions may develop up to several days post administration; in such case, a physician should be consulted immediately. Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, anuria, diabetes mellitus, homozygotic sickle cell disease, or monoclonal gammopathy (multiple myeloma, Waldenströms macro-globulinaemia), particularly when large doses are administered. Serious renal effects, including acute renal failure, may occur in these patients. Preparatory dehydration is dangerous and may contribute to acute renal failure. Iodine-containing contrast media may also be hazardous in patients with hyperthyroidism or with autonomous areas of the thyroid gland. In patients with phaeochromocytoma a premedication with alpha-blockers is advisable when the contrast medium is administered intravascularly due to the risk of a hypertensive crisis. Serious neurologic events have been observed following direct injection into cerebral arteries or vessels supplying the spinal cord, or in angiocardiography due to inadvertent filling of the carotids. General anaesthesia may be indicated in selected patients. However, a higher incidence of adverse reactions has been reported in these patients, probably due to the hypotensive effect of the anaesthetic. In angiographic procedures, the possibility of dislodging plaque or damaging or perforating the vessel wall should be considered during catheter manipulation and contrast medium injection. In patients with advanced atherosclerosis, serious hypertension, cardiac decompensation, senility, preceding cerebral thrombosis or embolism, special caution should be exercised. Cardiovascular reactions as bradycardia, rising or falling of blood pressure may occur more often. Angiography should be avoided whenever possible in patients with homocystinuria due to an increased risk of thrombosis and embolism. OPTIRAY® should be injected with caution to avoid perivascular application. However, significant extravasation of OPTIRAY® may occur especially during the use of power injectors. Generally, it is tolerated without substantial tissue injury applying conservative treatment. However, serious tissue damage (e.g. ulceration) has been reported in isolated cases requiring surgical treatment. **For interactions and specific warnings**, please refer to summary of product characteristics. **Summary of safety profile:** Adverse reactions following the use of OPTIRAY® formulations are generally independent of the dose administered. Usually, they are mild to moderate, of short duration and resolve spontaneously (without treatment). However, even mild adverse reactions may be the first indication of a serious, generalized reaction that can occur rarely after iodinated contrast media. Such serious reactions may be life-threatening and fatal, and usually affect the cardiovascular system. Most adverse drug reactions to OPTIRAY® formulations occur within minutes after administration, however contrast related hypersensitivity reactions may occur with a delay of some hours up to several days. **Adverse reactions may be classified as follows:** Hypersensitivity or anaphylactoid reactions are mostly mild to moderate with symptoms like rash, pruritus, urticaria and rhinitis. However, serious reactions may occur. Serious anaphylactic reactions generally affect the cardiovascular and respiratory system. These may be life-threatening and include anaphylactic shock, cardiac and respiratory arrest, or pulmonary oedema. Fatal cases were reported. Patients with a history of allergic reactions are at increased risk of developing a hypersensitivity reaction. Other type 1 (immediate) reactions include symptoms like nausea and vomiting, skin rashes, dyspnoea, rhinitis, paraesthesia or hypotension. Vasovagal reactions e.g. dizziness or syncope which may be caused either by the contrast medium, or by the procedure. Cardiologic side effects during cardiac catheterisation e.g. angina pectoris, ECG changes, cardiac arrhythmias, conductivity disorders, as well as coronary spasm and thrombosis. Such reactions are very rare and may be caused by the contrast medium or by the procedure. Nephrotoxic reactions in patients with pre-existing renal damage or renal vasopathy, e.g. decrease in renal function with creatinine elevation. These adverse effects are transient in the majority of cases. In single cases, acute renal failure has been observed. Neurotoxic reactions after intra-arterial injection of the contrast medium e.g. visual disorders, disorientation, paralysis, convulsions, or fits. These symptoms are generally transient and abate spontaneously within several hours or days. Patients with pre-existing damage of the blood-brain barrier are at increased risk of developing neurotoxic reactions. Local reactions at the injection site may occur in very rare cases and include rashes, swelling, inflammation and oedema. Such reactions occur probably in most cases due to extravasation of the contrast agent. Extended paravasation may necessitate surgical treatment. Extravasation can cause serious tissue reactions including blistering and skin exfoliation, the extent of which is dependent on the amount and strength of the contrast solution in the tissues.

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For your specific information, please contact your local Guerbet representative.
Date of (partial) revision of the text: March 2016

Guerbet
Contrast for Life

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