Guerbet

SPECTRUM MEDICAL IMAGING CO.

Optiray®
loversol

AGILITY

for seamless integration into your interventional cardiology practice

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

After coronary angiography [1]

After PCI [1]

High-risk patients* after coronary angiography or PCI [2,3]

INCREASED IN-HOSPITAL COMPLICATIONS AND MORTALITY [4-6]

Major adverse cardiac event (MACE)
15 fold increase *vs.* no CIN [4]

Persistant renal damage
2,5 fold increase *vs.* no CIN [5]

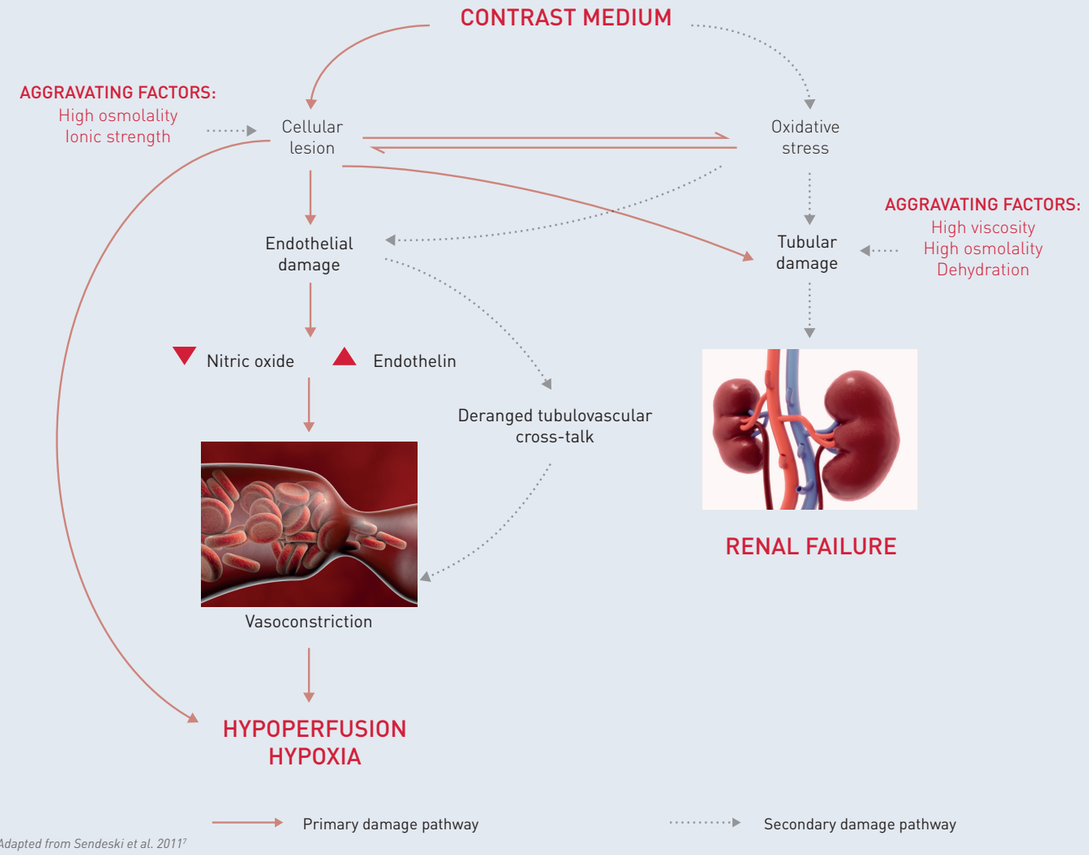
In-hospital mortality
5 fold increase *vs.* no CIN [6]

1-year mortality
4 fold increase *vs.* no CIN References cited in 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



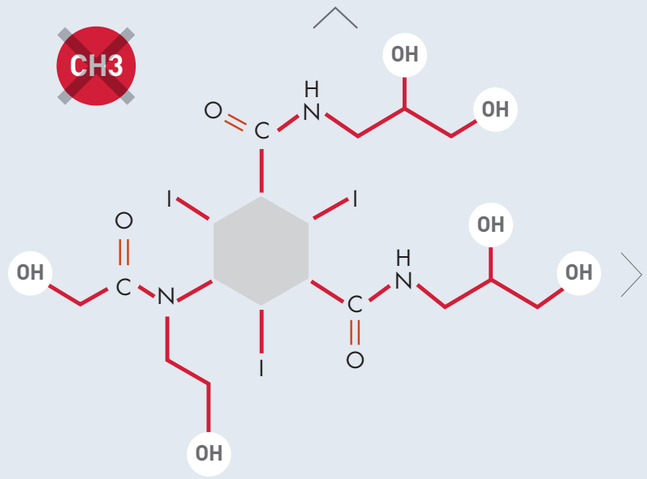
Adapted from Sendeski et al. 2011 [7]

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 classified as low osmolality contrast media [9-11]

OPTIRAY® CHEMICAL STRUCTURE [9]



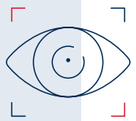
The highest hydrophilicity in iodinated contrast media [11]

Low osmolality [10]
Hinders fluids shifting from the intracellular to extracellular space and thus hinders cell dehydration [8]

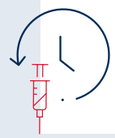
Potential benefits of low viscosity contrast agents

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]

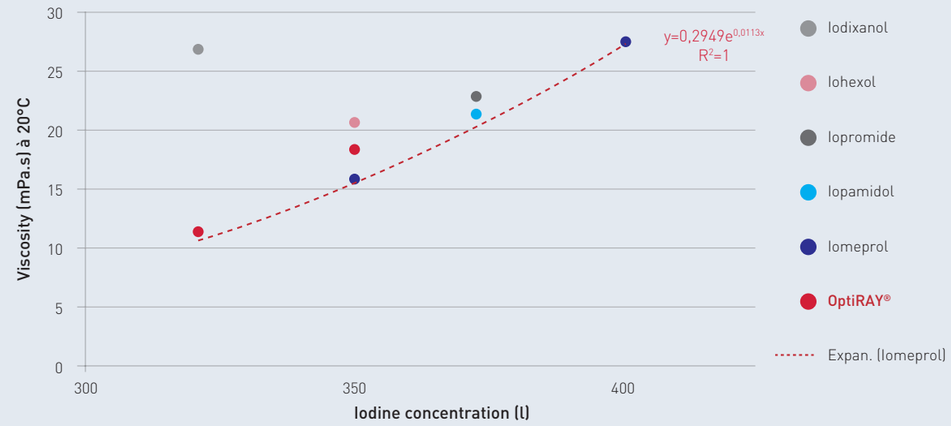


Enables to reduce infusion time vs. fluids with high viscosity in same infusion conditions [12]

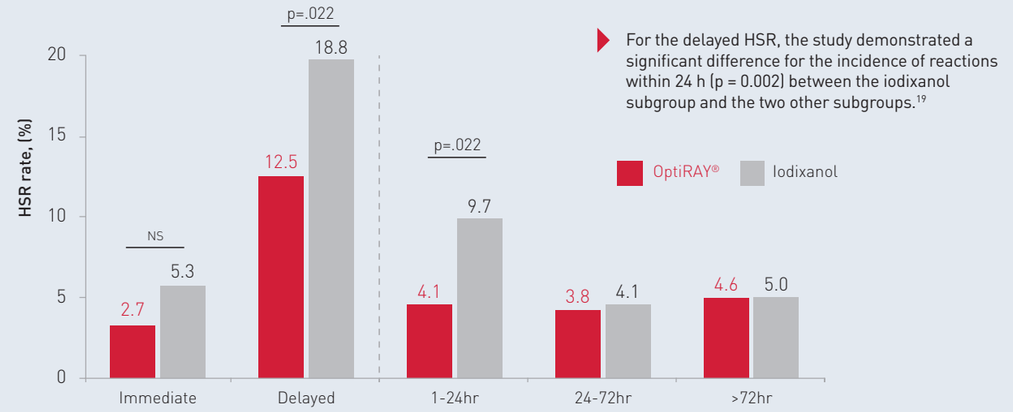
References: 8. Thomsen HS. Management of acute adverse reactions to contrast media. In: Thomsen HS, editor. Contrast Media: Safety Issues and ESUR Guidelines. Heidelberg, Springer;2006. pp. 19-25. **9. Optiray®** prescribing information, available on complete SmPC. **10.** Voeltz MD, et al. The Important 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.

Optiray® 320 and **Optiray® 350** have lower viscosity compared with iodixanol 320 and the lowest range of viscosity within iodinated contrast products [9,14-18]

RELATION BETWEEN IODINE CONCENTRATION AND VISCOSITY [9,14-18]



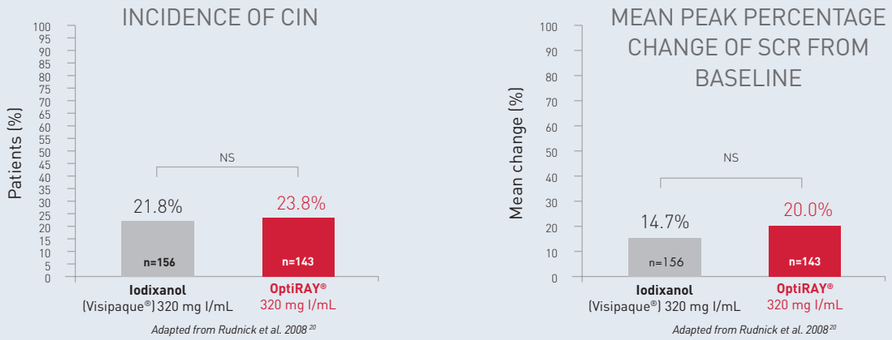
Optiray® 320 is associated with a significant lower delayed hypersensitivity reactions (HSR) incidence when compared to iodixanol in patients undergoing coronary angiography [19]



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.** Sohn KH et al. Immediate and delayed hypersensitivity after intra-arterial injection of iodinated contrast media: a prospective study in patients with coronary angiography. Eur radiol 2019; April 1: 1-8.

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]



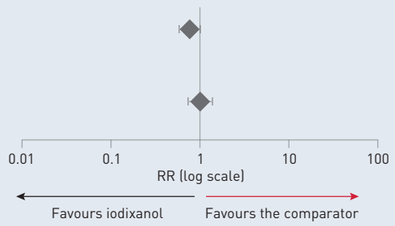
Adapted from Rudnick et al. 2008 [20]

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.

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

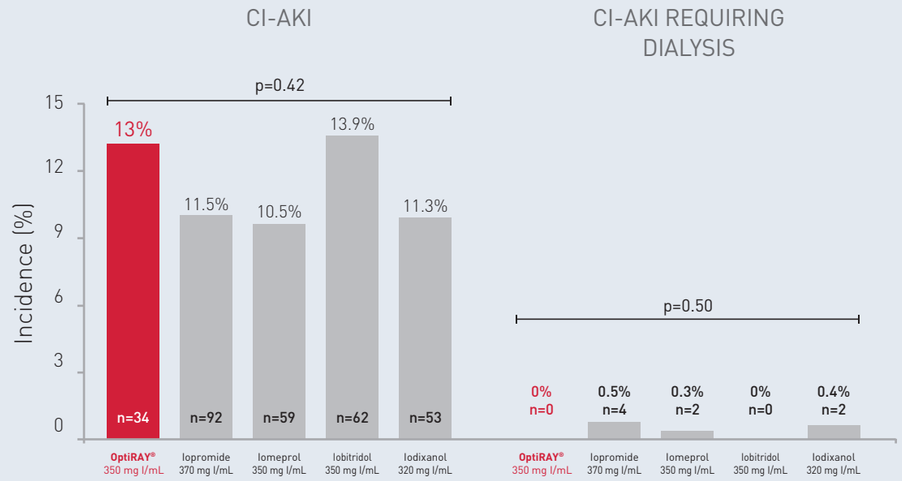
RELATIVE RISK (RR) OF CIN 21.*,†

	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)



- 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 difference in the risk of CIN was observed among various types of low-osmolar contrast media in the reviewed studies [23]

There is no benefit proven of IOCM use to prevent contrast-induced renal failure [22]



- LOCM **Optiray®**, iopromide, iomeprol and iobitridol were associated with similar risk of CI-AKI compared with IOCM iodixanol in the Azzalini study.
- None of the patients who received **Optiray®** required dialysis even if it was linked to the highest CTO PCI rate and one of the highest contrast volume per procedure.
- Independent predictors of CI-AKI are age, left ventricular ejection fraction (LVEF), baseline hemoglobin, hypotension during/before PCI, acute coronary syndrome (ACS) and contrast volume.

The study by Azzalini et al. is a single-center retrospective study comparing the risk of contrast-induced acute kidney injury (CI-AKI) after percutaneous coronary intervention (PCI) between iso-osmolar contrast medium (IOCM) and low-osmolar contrast media (LOCM) in 2648 patients. [22]

***** 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.

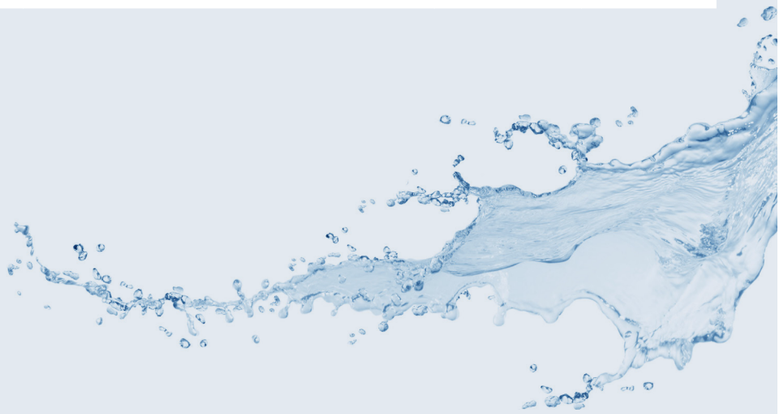
† In the meta-analysis, only one study involved **Optiray®**, weighing 14.5% of the population in the comparison of iodixanol with low-osmolar contrast media pooled together and 19.5% in the comparison of iodixanol with low-osmolar contrast media other than iohexol.

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].

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.** Azzalini L et al. Incidence of contrast-induced acute kidney injury in a large cohort of all-comers undergoing percutaneous coronary intervention : Comparison of five contrast media. Int J Cardiol. 2018 ; 273 : 69-73. **23**. Eng J, et al. Comparative Effect of Contrast Media Type on the Incidence of Contrast-Induced Nephropathy. Ann Intern Med. 2016;164:417-424.

BOTH LOW-OSMOLAR AND ISO-OSMOLAR CONTRAST AGENTS ARE RECOMMENDED BY INTERNATIONAL GUIDELINES [24,25,26]

SCIENTIFIC ASSOCIATION	RECOMMENDATION FOR CIN PREVENTION IN AT-RISK PATIENTS	GRADE OF RECOMMENDATION	LEVEL OF EVIDENCE
Ref [24]	In patients with moderate to severe CKD, use of low-osmolar or iso-osmolar contrast media, is associated with the highest grade of recommendation and level of evidence.	I	A*
Ref [25]	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.	I†	B†
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.	I¶	B¶



***** 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. AHA = American Heart Association. CKD = chronic kidney disease. CI-AKI = contrast-induced acute kidney injury. 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. SCAI = Society for Cardiovascular Angiography and Interventions. Scr = serum creatinine.

References: 24. Neumann FJ, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40, 87–165. **25.** Kidney Disease: Improving Global Outcomes. Kidney Inter Suppl. 2012;2:1-138. **26.** Kushner FG, et al. 2009 Focused Updates: STEMI and PCI Guidelines. Catheter Cardiovasc Interv. 2009;74:E25-E68.

Optiray® - HIGH DIAGNOSTIC IMAGE QUALITY [27] FOR CARDIAC PROCEDURES

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

Differences between South African and European cardiac patients'care
https://www.incathlab.com/en/lives/1-coronary/71-pci/2074-differences-between-south-african-and-european-cardiac-patients-care

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 except selective cerebral angiography. ▸ 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 including digital subtraction angiography (DSA) 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, peripheral, and abdominal arteriography,including digital subtraction angiography (DSA), in adults. ▸ Indicated for contrast enhanced computed tomographic imaging of the head and body, venography, and intravenous excretory urography. ▸ Indicated in children for cerebral, peripheral and abdominal angiography, including digital subtraction angiography (DSA), computed tomography of the head and body, 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.

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 [27].

9. Optiray® prescribing information, available on complete SmPC. 27. 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 be coupled with our injector illumena® Néo, its consumables and our innovative digital solutions to provide an interconnected solution for ANGIO-CARDIAC and ANGIO-PERIPHERAL imaging

THE TAILORED INTERCONNECTED SOLUTION THAT MAKES THE DIFFERENCE IN YOUR CATH LAB

- An easy-to-use and updated contrast delivery system perfectly suited to contrast medium with relevant physicochemical properties to upgrade your cath lab routine
- SIMPLE and FUNCTIONAL, developped with CARE in mind, illumena® Néo, the multi-mode injector you can trust
- Good safety profile combined to a high image quality to optimize your interventional cardiology procedure
- A solution that will simplify your daily work

UNIK

Tailored interconnected solutions driving your journey to excellence

Contrast&Care® is a medical device intended for use by healthcare professionals only. It allows imaging centers to collect, archive, view and share patients' injection data, including data concerning contrast products, adverse events, injector activity, data on the estimated eGFR and other pre-exam alerts, such as previously reported allergies. Contrast&Care® also provides options to review protocols, create protocol libraries, and visualize analytics data and trends relating to injection activity and contrast product usage. Class I/CE Manufacturer: Medex

Contrast&Care®+ is a medical device for use by healthcare professionals only. It enables imaging centers to collect, archive, review, and share patient injection data. This data can include contrast media details, associated disposables, adverse events, injector activity, history of previous contrast media administration, eGFR information, and other pre-exam alerts, such as previously reported allergies. It also provides features to review protocols, create protocol libraries, send injection protocols to compatible injectors, visualize analytics and trends related to injection activity and contrast media usage. Class I/CE Manufacturer: Medex.

KPI - Key Performance Indicators

eGFR - Estimated Glomerular Filtration Rate

Contrast&Care® is a trademark of Guerbet.

For complete information about precautions and optimal usage conditions, we recommend consulting the instruction for use supplied with the device or by your local Guerbet representative(s). For use only in countries with applicable health authority registrations.

illumena Néo Contrast Media Injectors is a medical device intended for use by qualified healthcare professionals, it is designed to inject a radiopaque contrast medium into the vascular system for Angiographic or CT procedures as prescribed by qualified health care professionals. Contraindications for the use of this device are determined by the prescribing physician at the time of use based upon the contrast media package inserts. Class IIb/CE. TÜV SÜD 0123. Manufacturer: Liebel-Flarsheim Company LLC. EC Rep: Guerbet. For complete information about precautions and optimal usage conditions, we recommend consulting the instructions for use supplied with the device or by your local Guerbet representative(s). For use only in countries with applicable health authority registrations. LF™ & illumena® are registered trademarks of Guerbet Group or its affiliates. Patents pending and issued patents. © Copyright 2015.

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® Néo.

illumena® Néo
+ certified(*) consumables

CERTIFIED by Guerbet

Contrast&Care®

Injection management software solution

Simplify administrative tasks thanks to automated interfaces between with your HIS (EMR / RIS / PACS)
Support informed decisions thanks to comprehensive and customizable dashboards

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

(*) certified by guerbet as compatible on guebet injectors ***** data on file

OPTIRAY™ is a sterile, non-pyrogenic, aqueous solution intended for intravascular and subarachnoid administration.

Composition:(*) OPTIRAY™ 160 Ioversol, 339 mg/ml, which is equivalent to 160 mg/ ml of organically bound iodine. OPTIRAY™ 240 Ioversol, 509 mg/ml, which is equivalent to 240 mg/ ml of organically bound iodine. OPTIRAY™ 300 Ioversol, 636 mg/ml, which is equivalent to 300 mg/ml of organically bound iodine. OPTIRAY™ 320 Ioversol, 678 mg/ml, which is equivalent to 320 mg/ml of organically bound iodine. OPTIRAY™ 350 Ioversol, 741 mg/ml, which is equivalent to 350 mg/ml of organically bound iodine.

Indications (*): OPTIRAY™ non-ionic X-ray contrast medium for diagnostic use only.

OPTIRAY™ 350 is indicated in adults for angiography, including intra-arterial, digital subtraction angiography (IA-DSA), throughout the cardiovascular system, except selective cerebral angiography. OPTIRAY™ 350 is also indicated for contrast enhanced computed tomographic imaging of the head and body, intravenous excretory urography, intravenous digital subtraction angiography and venography. OPTIRAY™ 350 is indicated in children for angiocardiography.

OPTIRAY™ 320 is indicated in adults for angiography, including digital subtraction angiography (DSA), throughout the cardiovascular system. The uses include but are not limited to cerebral, coronary, peripheral, visceral and renal arteriography, venography, aortography, and left ventriculography. OPTIRAY™ 320 is also indicated for contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography. OPTIRAY™ 320 is indicated in children for angiocardiography, contrast enhanced computed tomographic imaging of the head and body, and intravenous excretory urography.

OPTIRAY™ 300 is indicated for cerebral, peripheral, and abdominal arteriography, including digital subtraction angiography (DSA), in adults. OPTIRAY™ 300 is also indicated for contrast enhanced computed tomographic imaging of the head and body, venography, and intravenous excretory urography. OPTIRAY™ 300 is indicated in children for cerebral, peripheral and abdominal angiography, including digital subtraction angiography (DSA), computed tomography of the head and body, and intravenous excretory urography.

OPTIRAY™ 240 is indicated for cerebral, peripheral, and abdominal angiography, including intra-arterial, digital subtraction angiography (IA-DSA), and venography in adults. OPTIRAY™ 240 is also indicated for contrast enhanced computed tomographic imaging of the head and body and intravenous excretory urography. OPTIRAY™ 240 is indicated in children for cerebral, peripheral and abdominal angiography, including digital subtraction angiography (DSA), computed tomography of the head and body, and intravenous excretory urography. OPTIRAY™ 240 is indicated for subarachnoid administration in adults for lumbar, thoracic and cervical myelography, in some countries.

OPTIRAY™ 160 is only indicated for intra-arterial digital subtraction angiography (IADSA) in adults.

Posology and Method of Administration (*): The dosage may vary between 1 ml and 150 ml, maximum total dose 250 ml or less depending on the indications, the composition of OPTIRAY, the patient's factors and other technical factors. **Please refer to the Summary of Product Characteristics for the recommended dosage schedule.**

Contraindications: Hypersensitivity to ioversol ot to any of the excipients. Manifest hyperthyroidism.

Special Warnings and Precautions for Use: Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients and in susceptible nondiabetic patients (often elderly with pre-existing renal disease). Patients should be well hydrated prior to and following the administration of Optiray. The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See Adverse Reactions). Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients administered Optiray. Early or late manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Increased risk is associated with a history of previous reaction to a contrast medium, and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities. The occurrence of severe idiosyncratic reactions has prompted the use of several pre-testing methods. However, pre-testing cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pre-testing in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Pre-medication with antihistamines or corticosteroids to avoid or minimize possible allergic reaction in such patients should be considered. Reports indicate that such pre-treatment does not prevent serious life-threatening reactions but may reduce both their incidence and severity. General anesthesia may be indicated in the performance of some procedures in selected patients. However, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia. In angiographic procedures, the risk of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are suggested. Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism. Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load. About procedural risks, selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure. Caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease. **Specific warnings related to Intravascular administration:** Caution must be exercised in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, severely impaired renal function, renal and hepatic disease, multiple myeloma or other paraproteinemia, anuria, pheochromocytoma, sickle cell disease and in neonates. Meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. **Specific warnings related to Subarachnoid administration:** Myelography should not be performed in the presence of significant local or systemic infection where bacteremia is likely or when lumbar or cervical puncture is contraindicated. Myelography should be performed only in hospitalized patients under close medical observation, which is to be continued for 24 hours following the procedure.

Gravitational displacement of a concentrated bolus of Optiray above the level of C1 and especially into the intracranial subarachnoid spaces is to be avoided. Caution must be exercised in patients with history of seizure, epilepsy and elderly patients. **Please refer to the Summary of Product Characteristics for complete information about specific warnings.**

Interactions with other medicinal products and other forms of interaction: With metformine, vasopressor and the results of protein-bound iodine (PBI) and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. Please refer to summary of product characteristics. **Fertility, pregnancy and lactation:** There are no adequate and well controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed. Although it has not been established that adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

Effects on ability to drive and use machines: There is no known effect on the ability to drive and operate machines. However, because of the risk of early reactions, driving or operating machinery is not advisable for 30 to 60 min following administration.

Undesirable effects: Adverse reactions following the use of OPTIRAY™ **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. Injections of contrast media are very commonly associated with sensations of warmth, and commonly associated with pain.

Adverse reactions may be classified as follows: • Hypersensitivity or anaphylactoid reactions are mostly mild to moderate with symptoms like rash, pruritus, urticaria, rhinitis and blister. These symptoms may occur independent of dose and route of administration and may be the first signs of an evolving shock with symptoms like pronounced decrease in blood pressure, tachycardia, dyspnoea, pallor and decrease in consciousness. Fatal cases were reported. • Vasovagal reactions with symptoms ranging from dizziness and hypotension to syncope. Vasovagal reactions may be caused either by the contrast media or by the procedure. • Cardiologic side effects during cardiac catheterization may include ECG changes, arrhythmia, conductivity disorders as well as coronary spasm. Such reactions may be caused by the contrast media or by the procedure. • Nephrotoxic reactions with acute renal failure may occur in patients with pre-existing renal damage. • Neurotoxic reactions after intra-arterial injection of the contrast medium like confusion, visual disorders, convulsions or fits. The symptoms are generally transient and abate spontaneously within several hours. • Local reactions at the injection site may occur and include rashes, swelling, inflammation and edema. Such reactions occur probably in most cases due to extravasation of the contrast agent. Extended paravasation may necessitate surgical treatment. For subarachnoid administration: Any adverse reactions known to occur with the intravascular use of OPTIRAY™ can also occur during myelography, especially those which originate in the CNS. The most commonly observed adverse reaction was headache, which had an incidence of 8.6%. **Overdose:** The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

Pharmacological properties: Pharmacotherapeutic group: water-soluble, nephrotropic, low-osmolar X-ray contrast media ATC code: V08AB07.

Incompatibilities: No medicinal product should be mixed with OPTIRAY™.

Nature and content of container: (*) OPTIRAY™ is supplied in glass bottles and plastic pre-filled syringes.

Marketing authorization holder: (*) Information: Guerbet – BP 57400 – F-95943 Roissy CdG cedex - France. Tel: 33 (0) 1 45 91 50 00. Date of revision: 13/12/2020

For current and complete prescribing information refer to the local Summary of Product Characteristics (SmPC) and /or contact your local Guerbet organization.

(*) Marketing Authorization Information: The marketing authorization holder, number and date of approval may differ from one country to another. Volume, presentation, indication and Posology and Method of Administration may also differ.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

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