Mallinckrodt has pioneered the development of single-use, pre-filled contrast medium syringes which benefit both the patient and user in terms of safety and hygiene.

This review document is designed to assist medical professionals in weighing the value of a contrast medium in a ready-to-use pre-filled syringe.

For more information visit www.mallinckrodt.com
What is Optiray™?

Mallinckrodt’s Optiray™ (ioversol) is a non-ionic contrast medium, supplied in vials and in single use pre-filled syringes.

Ioversol has no methyl groups (CH3-) with six hydroxyl groups (-OH) symmetrically arranged around the tri-iodinated benzene ring.

Optiray™ (ioversol) has been proven to cause few adverse drug events when administered to patients.\(^1\)^\(^2\)

In addition, as each Optiray™ syringe is pre-filled, it is not necessary for the healthcare professional to transfer the contrast medium into an empty syringe. This means that:

- The process is faster, leaving more time for patient care\(^3\)
- Each patient benefits from a single-use, closed system
Putting patients first

Optiray™ is the most hydrophilic non-ionic, monomeric X-ray contrast medium on the market.4,5,6

In 2009 Dr. Tatsuya Gomi from Toho University Ohashi Hospital published his research comparing differences in acute adverse reactions among five low-osmolar, non-ionic, iodinated contrast media.

The study found that Optiray™ was the contrast medium with the lowest incidence of acute adverse reactions.1

McGaughey et al. showed in their study that Optiray™ is well tolerated and safe when used for cardiac interventional procedures.2

Table 2
Adapted from Gomi et al.

<table>
<thead>
<tr>
<th></th>
<th>Average Incidence</th>
<th>% of patients with acute adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iomeprol</td>
<td>1.751</td>
<td>3.9</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>1.805</td>
<td>3.5</td>
</tr>
<tr>
<td>Ioversol</td>
<td>1.886</td>
<td>2.2</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>1.892</td>
<td>2.0</td>
</tr>
<tr>
<td>Iohexol</td>
<td>1.864</td>
<td>1.8</td>
</tr>
</tbody>
</table>

p<0.01    Iomeprol vs iopamidol, iohexol or ioversol
p<0.01    Iopamidol vs iohexol or ioversol
Tolerability

Neural tolerability
As the most hydrophilic of the marketed, monomeric X-ray contrast media, Optiray™ contrast medium displayed good neural tolerability in animal experiments.7,8

In a preclinical comparison of intracisternal toxicity with iohexol and iopamidol, Optiray™ contrast medium had the lowest toxicity.9

Cardiac tolerability
Cardiac tolerability of contrast media is a major issue, especially during ventriculography and coronary arteriography procedures. Hirshfeld et al10 and McGaughey et al2 have demonstrated in their respective clinical trials that Optiray™ does not induce any significant ECG nor hemodynamic disturbance.

Renal tolerability
With no detectable difference in serum creatinine and blood urea nitrogen levels between physiological saline and Optiray™ contrast medium, good renal tolerability was demonstrated in healthy subjects.11

A multicenter double blind randomized trial in at risk patients (VALOR trial) did not show any statistical significant difference in CIN incidence between patients administered ioversol vs patients who received ioxixanol.12

Furthermore, Heinrich et al13 have published their meta-analysis including 25 clinical studies and involving 3,270 patients undergoing either an IV CT scan or an intra-arterial procedure. The authors concluded that LOCM did not significantly induce more risk of CIN in the evaluated patients’ population. A sub-analysis of this study revealed that no statistical difference could be found when Optiray was compared to ioxixanol as regards the CIN incidence.

The American College of Cardiology and American Heart Association (ACC-AHA) as well as the European College of Cardiology (ESC) have updated their respective Guidelines as regards the choice of contrast media for intravascular arterial cardiac procedures in relation with the risk of CIN in patients with chronic kidney disease (CKD).14,15

Their conclusions were that both isosmolar and LOCM (except iohexol and ioxaglate in the American Guidelines) are recommended for being administered in patients undergoing coronary angiography and revascularization interventional procedures.14,15

References
3. Lafuma A. et al., Comparison of the time to prepare contrast media injection in CT scan exam with prefilled syringes and bottles in 7 European countries. Value Health. The Journal of the International Society for Pharmacoeconomics and Outcomes Research, 2009; vol.12, N 7: p A254
9. Raitson W. et al., The acute and subacute toxicity of ioversol (Optiray*) in laboratory animals. Invest. Radiol., 1989; 24: S3-S9
About Mallinckrodt

Mallinckrodt is a $2 billion global company that develops, manufactures, markets and distributes specialty pharmaceutical products and diagnostic imaging agents.

We combine more than 145 years of expertise with the determined focus needed to solve the complex pharmaceutical challenges of today. Whether it's the production of medicines for pain or development of state-of-the-art imaging technology, we are working to make complex products simpler, safer, and better for patients.

As the new Mallinckrodt, meeting the needs of you and your patients for contrast media, delivery systems and nuclear medicine products is our priority.
COMPOSITION: OPTIRAY™ 240 mg iodine/ml, solution for injection or infusion, 509 mg/ml ioversol. OPTIRAY™ 300 mg iodine/ml, solution for injection or infusion, 636 mg/ml ioversol. OPTIRAY™ 320 mg iodine/ml, solution for injection or infusion, 678 mg/ml ioversol. OPTIRAY™ 350 mg iodine/ml, solution for injection or infusion, 743 mg/ml ioversol. INDICATIONS: OPTIRAY™ is a 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 sestamibi SPECT (Gallium 67m), myocardial perfusion imaging 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. POSSOLOGY 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, the active substance, or to any of the excipients. Manifest hyperthyroidism. SPECIAL WARNINGS AND PRECAUTIONS FOR USE. Serious or fatal reactions have been associated with the administration of iodinated X-ray contrast media. It is of utmost importance to be completely prepared to treat any contrast medium reaction. Such procedures should be performed 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, the patient should be observed and emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. 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. A higher incidence of such reactions has been observed in patients with a history of previous intolerance reactions to other contrast media, or any history of asthma, allergy or hypersensitivity. In such patients, the benefit should clearly outweigh the risks. 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, may be more accurate than pre-testing in predicting potential adverse reactions. Pre-medication with antihistamines and corticosteroids to avoid or minimise allergic reactions should be considered. General anaesthesia may be indicated in the performance of some procedures in selected patients. 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. First injections to ensure proper catheter placement are recommended 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. 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. The patient should also be informed that allergic reactions may develop up to several days post administration; in some in vivo studies. For this reason, meticulous angiographic techniques are recommended. Similar results were found in one study for Optiray. 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. Mild discomfort, including sensation of heat or cold, pain during the injection, and/or transient taste perversion, was noted in 10% to 50% of patients. Other side effects such as urticaria or erythema (0.3%), and vomiting (0.1%). All other events occurred in less than 0.1% of the patients. 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 anaphylactik 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 catherisation 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. LEGAL STATUS: Prescription only. MARKETING AUTHORISATION HOLDER: Mallinckrodt Deutschland GmbH Josef-Dietzgen-Str. 1, 53773 Hennef DATE OF REVISION OF THE TEXT: August 2013