

Scientific Collection 04

The ACTIVE study

Comparison of the Effects on Renal Function of Iomeprol-400 and Iodixanol-320 in Patients with Chronic Kidney Disease Undergoing Abdominal Computed Tomography

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Objective

Patients with pre-existing chronic kidney disease (CKD) are at greater risk of experiencing contrast induced nephropathy (CIN) following injection of iodinated agents . This study compared the effects of iomeprol-400 (lomeron® 400, Bracco Imaging, Milan, Italy) and lodixanol-320 (Visipaque™ 320, GE Healthcare, Chalfont St. Giles, United Kingdom) on the renal function of patients with pre-existing moderate-to-severe CKD undergoing contrast-enhanced multidetector CT (CE-MDCT).

Study Design

This was a prospective, multicenter, double blind, randomized, parallel group comparison of iomeprol-400 and iodixanol-320 in renally impaired patients receiving relatively high intravenous (IV) doses (40gl) of the two contrast media. Incidence of Contrastinduced Nephropathy (CIN): All Patients (*n* = 148)



lodixanol-320 (n = 72)



Incidence of CIN: Patients with creatinine clearance <40mL/min and/or SCr \ge 2.0 mg/dL (n = 73)



Results

- The CIN analysis population consisted of 148 evaluable patients, of whom 76 received iomeprol-400 and 72 iodixanol-320.
- The two study groups were comparable at baseline with regard to age, gender, hydration status, baseline SCr and CrCl values. However, the iomeprol-400 group had a significantly higher proportion of patients with CKD and diabetes mellitus (p = 0.02).
- A total of 5 patients (6.9 %) receiving iodixanol-320 and none of the 76 patients (0%) receiving iomeprol-400 experienced an increase in SCr ≥0.5 mg/dL from baseline CIN (p = 0.025)
- Relative rises in SCr of \geq 25% and relative CrCl decreases of \geq 25% occurred with similar frequency in both groups (p > 0.05)
- In the subset of patients with CrCl <40 mL/min and SCr >2.0 mg/dL, no cases of CIN (0/39) were detected after the administration of iomeprol-400, independently of the CIN endpoint used, while the rate of CIN after iodixanol-320 was 11.8% (4/34) using the primary endpoint (*p* = 0.04), and 5.9% (2/34) using the secondary CIN endpoints
- The difference in mean change in SCr between the two groups was statistically significant (p = 0.017).





Patients and methods

- Patients: adult patients with moderate-to-severe CKD, i.e. serum creatinine $(SCr) \ge 1.5 \text{ mg/dL}$ and/or creatinine clearance (CrCl) < 60 mL/min.
- Type of examination: CE-MDCT of the liver.
- Dose: equi-iodine doses (40 gl) of iomeprol-400 or iodixanol-320, both injected intravenously at a rate of 4mL/sec, followed by a 20ml bolus of saline solution.
- CIN lab parameters: SCr was measured at screening, baseline and 48–72 hours post-dose.
- Blinded review: A Renal Safety Review Board, comprised of 3 medical experts, reviewed the renal safety data of each subject in a blinded manner.
- Primary CIN endpoint: increase in SCr \ge 0.5 mg/dL from baseline to post-dose, in the total population and in patients with baseline CrCl <40 mL/min and SCr \ge 2.0 mg/dL.
- Secondary CIN endpoints: increase in SCr \ge 25% from baseline; decrease in CrCl \ge 25% from baseline; mean changes in SCr from pre-dose to post-dose.



Key messages

iomeron[®]

- Contrast induced nephropathy is a recognized complication following the administration of iodinated contrast agents to patients with chronic kidney disease.
- Based on the results of this study the authors concluded:

'The incidence of CIN was significantly higher after the IV administration of iodixanol-320 than iomeprol-400 in patients with moderate-to-severe chronic kidney disease. The mean increase in SCr from baseline was also higher in patients receiving iodixanol. Characteristics of the individual contrast agents other than osmolality may be important in causing nephrotoxicity.'



IERON ©: CORE SUMMARY OF PRODUCT CHARACTERISTICS NMME OF THE MEDICINAL PRODUCT IOMERON 150 mg/ml Solution for Injection, IOMERON 200 mg/ml Solution for Injection, IOMERON 250 mg/ml Solution for Injection, IOMERON 300 mg/ml Solution for Injection, IOMERON 350 mg/ml Solution for Injection, IOMERON 400 mg/ml Solution for Injection, OutLITATIVE AND QUANTITATIVE COMPOSITION 2

UMERIA INTERNA UMARINI INTER COMPOSITION (MERON 15 contains (quantity/10 mi): Active ingredient: lomeprol: 30.62 g, IOMERON 200 contains (quantity/10 mi): Active ingredient: lomeprol: 40.82 (OMERON 455 contains (quantity/10 mi): Active ingredient: lomeprol: 51.03 g, IOMERON 300 contains (quantity/10 mi): Active ingredient: lomeprol: 51.43 (DMERON 450 contains (quantity/10 mi): Active ingredient: lomeprol: 74.44, IOMERON 400 contains (quantity/10 mi): Active ingredient: lomeprol: 81.65

PHARMACEUTICAL FORM 2

ing the following physicochemical characteristics by lodine Strengths as below

lodine concentration mgl/mL	Osmolality MosmL/kg water (x ± s.t95)*	Viscosity MPa.s (x ± s.t95)	
	37° C	20°C 37°C	
150	301 ± 14	2.0±0.2 1.4±0.1	
200	362±17	3.1±0.2 2.0±0.2	
250	435±20	4.9±0.4 2.9±0.3	
300	521 ± 24	8.1±0.7 4.5±0.4	
350	618±29	14.5±1.1 7.5±0.6	
400	726±34	27.5±2.3 12.6±1.1	
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CLINICAL PARTICULARS 41

CLINICAL PARTICULARS
Therapeutic indications
This medicinal product is for diagnostic use only lomeron 150 Infusion urography, digital substraction phiebography, CT (brain and body) cavenosography,
intravenous and intraatrial DSA, ERCP, MCU, MCU in paediatrics. Iomeron 200 Peripheral phiebography, digital substraction phiebography, CT (brain and body),
cavenosography, intravenous and intraatrial DSA, ERCP, attrography, teptospation phiebography, collorging phy, retorgade preioureterography, mivelography, lomeron 250 Infusion urography, peripheral phiebography, CT (brain and body),
intravenous and intraatrial DSA, RCP, MCU, MCU in paediatrics, peripheral phiebography, CT (brain and body),
intravenous and intraatrial DSA, melocation rate paediatrics, peripheral phiebography, CT train and body), cavernosography,
intravenous and intraatrial DSA, angiocatiography (in adults and paediatrics), conventional selective corrany arteriography, tretorgade preioanteriography, Intravenous USA, angiocatidiography (in adults and paediatrics), conventional selective corrany arteriography, intravenous DSA, conventional angiocarby, interasterial DSA, angiocatidiography (in adults and paediatrics), conventional selective corrany arteriography, interventional coronay
retrograde urethrography, retrograde preioureterography, metro-aging phy, perior-salpingography, datarbigraphy, da 4.2 Posology and method of administration

russuoy and memoo or administration Instructions for use: Dosage and rate of administration may vary depending on the clinical question, the technique to be employed, the body area to be examined, the instrumentation, as well as on the age, body size, cardiac output and patient's clinical conditions in the CNS the imaging window has been shown to be up to 60 minutes after the administration. In the liver delayed imaging can be performed between 40 and 120 minutes following the injection, depending on the individual imaging needs.

Indication	Formulation mg (iodine)/ml	Proposed dosages	
Intravenous urography	250, 300, 350, 400	Adults: 50 - 150 ml	
		Newborns:3-4.8 ml/kg	
		Infants: 2.5–4 ml/kg	
		Paediatric patients: 1–2.5 ml/kg ^a	
Infusion urography	150	Adults: 250 ml	
		Paediatric patients ^a	
Peripheral phlebography	200, 250, 300	Adults: 10–100 ml. repeat as necessary ⁰	
		(10-50 mi upper extremities; 50-100mi iower extremities)	
Phlebography in DS	150,200	Adults: 10–100 ml. repeat as necessary	
		(10-50 mi upper extremities; 50-00 mi lower extremities)	
Ci brain	150, 200, 250, 300	Adults: 50–200 ml	
CT body	150 200 250 200 250 400	Paediatric patients a	
Crody	130,200,230,300,330,400	Paperlistric nationts ^a	
Cavernosography	150 200 300	Adults un to 100 ml	
Introveneus DCA	050,200,000	Adulta 100 000 ml	
Intravenous DSA	200, 300, 350, 400	Auulis: 100–200 MI Paediatric nations ^a	
Conventional angiography		r deulduite patientis	
Arteriography of upper extremities:	300.350	Adults ^b	
Arteriography of pelvis & lower extremities:	300, 350, 400	Adults ^b	
Abdominal arteriography:	300, 350, 400	Adults ^b	
Arteriography of descending aorta:	300, 350	Adults ^b	
Pulmonary angiography:	300, 350, 400	Adults: up to 170 ml	
Cerebral angiography:	300,350	Adults: up to 100 ml	
Paediatric arteriography:	300	Children: up to 130 mi ^a	
interventional:	300, 330, 400	Adults ⁻ Dadiatric nationts ^a	
Introortorial DSA		1 aculatile patients	
Cerebral	150 200 300 350	Adults: 30– 60 ml for general view:	
Colona.	100,200,000,000	5–10 ml for selective injections	
		Paediatric Patients ^a	
Thoracic:	200, 300	Adults ^b :20–25 ml (aorta)	
		repeat as necessary 20 ml (bronchial arteries)	
Aortic arch:	150,200,300,350	Adults	
Abdomen:	150,200,250,300	Aduits	
Aortography	150,200,300,350	Adults ^c	
Iransiumbar aortography	150,200,300	Aduits	
Peripheral arteriography:	150,200,250,300	Aduits: 5 – 1 U mi for selective injections up to 250ml Paediatric natients ^a	
Interventional:	150 200 300	Adults: 10-20 ml for selective injections up to 250ml	
interventional.	100,200,000	Paediatric natients a	
Angiocardiography:	300 350 400	Adultsb	
raigiooaraiSgraphiy.	000,000,000	Paediatric natients a	
Conventional selective coronary arteriography	300, 350, 400	Adults: 4–10 ml artery repeat as necessary	
ERCP	,,	150, 200, 300 Adults: up to 100 ml	
Arthrography	200, 300, 350	Adults: up to 10 ml per injection	
Hysterosalpingography	200, 300, 350	Adults: up to 35 ml	
Fistulography	300, 350, 400	Adults: up to 100 ml	
Discography	300 250 400	Adults: up to 4 ml	
Dacryocystography	300, 350, 400	Adults: 0.15–1.2 millerinjection	
Sialography	300, 350, 400	Adults: 1–3 ml per injection	
MCU		150 Adults: 100–250 ml	
	150	Paediatric patients: 40–210 mla	
Retrograde cholangiography	200, 300, 350	Adults: up to 60 ml	
Retrograde ureterography	200,300	Adults: 20–100 ml	
Retrograde pyelo-ureterography	200, 300	Adults: 10–20 ml per injection	
Myelography	200, 250, 300	Adults 200: 13–22 ml, 250 10–18 ml, 300 8–15 ml	

rding to body weight and age b = Do not exceed 250 ml. Single injection volume depends on the vascular area to be examined

c = Do not exceed350 ml It is desirable that solutions of radiopaque diagnostic agents for intravascular and intraffecal use should be at body temperature when injected. Before use, examine the product to assure that the container and closure have not been damaged. Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with steries givinges. If non-disposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents. AS Contra-indications hypersensitivity to the accide principle and to any of its ingredients. Intravascular administration There are no prevent escilute contraindications the use of non-ionic urrangiographic contraint edia. Investigations of the female genitalia are contraindicated in suspected or confirmed pregnancy and in cases of cache inflammation. Intratheeal administration commentation and instration or contraindicated is suspected or confirmed pregnancy and in cases of cache inflammation. Intratheeal administration compared to cent administration or conscipation of the principle and administration. Tratheeal administration contraindication equipment is contraindicated to expect the subject of the child administration or conscipation of the contraindicated or confirmed pregnancy and in cases of cache inflammation. Intratheeal administration content and diministration or conscipation of the contraindicated or confirmed pregnancy and in cases.

- Due to overdose considerations, immediate repeat myelography in the event of technical failure is contraindicated. 4.4 Special warmings and special precaution for use Special Warmings General for all administration routes Consideration of possible serious side effects, the use of iodinated contrast media should be limited to cases for which there is a precise need for a contrast examination. The need should be evaluated on the basis of the cilical status of the patient, in particular in relation to history of pathologies of the cardiovascular renal and/or hepatabiliary systems. The use of contrast media should be avoided in case of Walderstroem's paragreteriemia, and multiple myeloma and of advanced hepata and/or rend diseases. Cardioapiographic diagnostic procedures that involve the use of any radiogaue contrast media should be carried out in hostigatis where appropriate emergency facilities and personnel trained in the support to rendul values. Specific pathologue contrast media should be carried out in the specific pathete emergency facilities should be taken in patheters with supported that involve inc. succonstrictions, contisonics, et p. 1 in the radiology departments of public or private cilinics. Specific care should be taken in patheters with supported thrombosis, philebits, severe ischemia, local infection or attra-venous obstruction. Use in specific patients. Nonater, sindans, children. Young infants (ge < 1 user) escretions. Care should be taken in patientible to electrobic behaviored to more taken in the rearries in the environs obstruction. Use in specific patients. From the rearries in the rearries in the environs in the advance in patients. Nonater examination in the support to the advance in the patients in the advance in the support to the advance in the support to the supervision of the taken in patients. The support is the support of the patients in the support of the support of the support of the support of the supervision of the support of the support of the support of the s ariunisaminos, veacoasmicots, consignicas, etc.) in the radiology departments or public or private onics. Special care solutio de taken in patients with suspected intrombois, piblicits, severe ischeria, icola infection or arter-venue obstruction. • Use in specific patients. Nonates, infants, children, Noung infants (apl < 1) weat sepecially neorates, are particularly susceptible to electryle imbalances and haemodynamic alterations. Care should be taken regarding the dosage to be used, the details of the procedure and the patient's status. Electryl: The tedrep are al special risk of reactions due to Children Acoung infants (apl < 1) and extrasystoles are more likely to occur in these patients. The frequently encountered combination of neurological disturbances and severe vascular pathologies constitutes a service some combination. The probability of acute renal insufficiency is higher in these subjects. Women of Child-Bearing Netential, Appropriate investigations and measures should be taken when exposing women of child-bearing potential to any X-ray examination, whether with or without contrast medium. • Use in patients with specific pathologic conditions Hyperensitivity to Iodinated contrast media. Altergric disposition. It is operally agreed that advese reactions to iodinated contrast media are nore common in patients having a history of allergy. history of a reaction to iodinated contrast media, melangi have and the intervences appear mere views and toot allergy. Asthmatic patients. The risk of froctnosepasam, inducing reactions in asthmatic patients, is higher after contrast. Hyperthyroidism, nodular gotter. The small annout of free inorganic iodide that may be present in contrast media, melangi have solutions there effects as appear one evident in patients with higher Hyperthyrolism or gotter. There existing real in the specific pathologic conditions by the real display for the evident in patients with poertifyroidism or gotters induces in reported following administration of ionic contrast med





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 cspecially important in patients with severe a density in the d 4.5 Interaction with other medicinal products and other forms of interaction Epidural and intrathecal controstented are non-urrently administered when odmated contrast media are used, because orchostendost may promote and affect the signs and symptoms of arachnolitis, see 4.3 Contratications) Thyroid function tests. Following administration of iodinated contrast media, the capacity of the thyroid tissue to take up radiostopes for the diagnosts of the depend on other sets. Following administration, even longer in individual cases. The results of Protein Emingtion and radioactive iodine updates studies, which depend in other sets that the signs and symptoms of arachnolitis, see 4.3 Contratications) Thyroid duracters is reduced for up to two weeks, or even longer in individual cases. The results of Protein Emingtion of and radioactive iodine updates studies, which depend in other sets motions, e.g., 17 seas update and total or results of Protein Sagsy are not affected. Oral Cholecystographic Agents: Feence Itheraute here there are there and in other set instancion y test sets. Hot oral cholecystographic Agents: Feence Itheraute here are not advate and interfere with laboratory test sets. Hot oral cholecystographic contrast media. However, etherwite there are no advate and vell-controlled studies in prepanent normal results of Proteinas. Whenever, passable, radiotan exposure, etherwite Network to contrast media are porty excreted in human breast timik, and from experiment and unce in an interfere with laboratory test sets. Hot or betrast-ted basis. Whenever, passable, radiotan exposure, telending the case of the radio advate and the laborative sets and the taby.
- 4.7 Effects on ability to drive and use machines No data is available. However, given the rare possibility of delayed adverse reactions to contrast media, driving or using
- 4.8 Undesirable effects General The col indicated contrast media may cause untoward side effects. They are usually mild to moderate. However, mactines more serious reactions up to anaphyteatid shock, with possible faal outcome, may occur. In most cases reactions occur within minutes of dosing up. However, neactions may mainlest also later on up to 24 hours from the injection, depending on the administration route. Anaphyteast (anaphyteast) does any one paired to develop the serious reactions may mainlest also later on up to 24 hours from the injection, depending on the administration route. Anaphyteast (anaphyteast) further as long as 20. The patient complians of feeling abnormal, agitation, fushing, feeling hot, sweating increased, dicziness, lacrimation increased, rhinits, fajalations, paraesthesia, pruntus, head thrubobing, pharynoglanyngel pian and throat tightness, ophysiquia, coupt, sneecing, utricaria, erythema, and millo localised oedema or anjoineuroitic oedema and dys near low earling is the administration of the contrast medium must be discontinued immediately and, if needed, appropriate specific treatment ungently initiation, cyanois and loss of consciousness progressing to respiratory and/or cardiac arrest may result in death. These events can court indepation, cyanois and loss of consciousness progressing to respiratory and/or cardiac arrest may result in death. These events can court ungently initiated and progress cardio-pulmonary result to routic reactions involved provide cardiac arrest may result in death. These events can court ungently initiated avenues cardiac arrest may result in death. These events can court and/or spiros cardiac arrest may result in death. These events can court angly and require full and aggressive cardio-pulmonary result/or ungent cardiacarrest may result in death. These events can court angly and require full and aggressive cardio-pulmonary result/or cardiacarrest may result in death. These events can court angly and require full and aggressive cardio-pulmonary re voided for 24 hours following the administration.

	Common	Uncommon	Rare
Cardiovascular (mainly after cardiovascularprocedures/interventions)	Bradycardia, tachycardia, hypertension, hypotension		Vasodilatation, cyanosis, circulatory collapse
Nervous System	Asthenia, syncope, headache	Dizziness, paralysis, agitation	Tremor, muscle spasms, confusion, loss of consciousness, visual field defect, aphasia, convulsions, coma
Gastrointestinal system	Nausea	Vomitina	
Respiratory system	Dyspnoea, nasal congestion, laryngeal oedema	Ť	
Skin and Subcutaneous Tissue		Wheals, pruritus, rash	
General	Injection site warmth and pain, pallor	Back pain, chest pain, rigors,	Anaphylactoid reaction
		injection site haemorrhage, pyrexia, sweating increased	(characterized by cardiovascular, respiratory and cutaneous symptoms)
Renal and Urinary Disorders			Renal insufficiency, oliguria, proteinuria,
			blood creatinine increased

Some of these events may occur as a consequence of the procedure. Post Marketing Surveillance The following undesirable effects have been reported during
post-marketing in <2/11.0000 patients. Intravascular and intra-thecal administration: •Ceneral shock, malaise, failuge, hot thushes, flushing, cold sweat, Odness
local, taste abnormality, thirst, nijection site reaction. •Nervous system: hyperkinetic syndrome, encephalopathy paraysis, culculates, theysing pacti-marketing in <2/11.0000 patients. Intravascular and intra-thecal administration: •Ceneral shock, malaise, failuge, hot thushes, flushing, cold sweat, Odness
local, taste abnormality, thirst, nijection site reaction. •Nervous system: hyperkinetic syndrome, encephalopathy paraysis, culculates, displaysing, aleadin soft administration, anging bectris, editasplase, antrythmis,
ventricular or atrial finilation, tachycardia, palpitations, atrioventricular block, electrocardiogram abnormal, ST segment elevation. •Neperiatory irrest,
pulmorary odema, acute respiratory direstes, syndrome (APOS, b); torchospaam, astima, planyngal edicorders, binarbidenta para, salaray
hypersecretion, dysphagia, •Uogentali, urinary inconfinence, blood urea increased. •Senses parosmia + Eye disorders: binchees transient, visual disturbance,
conjunctivities, elevatoris, cultures administration to body cavities Blood
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amytase increase is common following EPOC "Hockscopic retrograde cholangiopannetadography, fare been described. The reactions
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ereported in cases of antrography and Istudy graphy issually represent Intalian marketing basing participations applications respirately direacting anyterity. Fare administration to dore exceess elevatores

- S PHARMACOLOGICAL PROPERTIES
 S Pharmacokinetic properties Pharmacotherapeutic category: Radiological contrast media: hydrosoluble, nephrotropic, low osmolality. ATC code: V08AB10 The active ingredient of Inerron formulations is iomeprol, NN-big2, 3-dihydrosyncry0)-5-{(hydrosynach)-methylamino]-2.4,6-tri-lodo-1,3-berzaneticarboxamide, a tri-lodinated for use in X-ray examinations.
 Pharmacokinetic properties Intravascular Administration The pharmacokinetic, tolerability and diagnostic efficacy of Iometron formulations containing up to 400 mp iodin/mic have been determined in health youtheres and patients requiring urgority, canopicanghic, angiorganghic, canopicanghic, angiorganghic, canopicanghic, angiorganghic, angiorganghi

5.3 Preclinical safety data

- 3Preclinical safety data clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction. sults from studies in rats, mice and dose demonstrate that iomeprol has an acute intravenous or intra-arterial toxicity similar to that of the other non-ionic contrast media, as well as a good systemic tolerability after repeated intravenous administrations in rats and dogs. LD50 of iomeprol in [dolena/kg and the relevant 95% confidence limits in animals are as follows: Intravenous administration: 19 (19 3-20.5) (mouse) 11 (53 (13-21.6) ((mouse)) Intracistemal administration: >1.1 ((rat) Intracerobid administration: 53 (4.64-7.25) (rat)

- IC3-05-2542, monocological administration 75 (4.6.46-7.25) (rat) PHARMACEUTICAL PARTICULARS List of excipients trometamol, hydrochloric acid (d=1.18), water for injection Incompatibilities Contrast media must not be mixed with other medicinal products, to avoid eventual incompatibilities. The second secon
- Incompatibilities Contrast media must not be mixed with other medicinal products, to avoid eventual in RATE parameters. Shell the 5 years Special precautions for storage Expiry date refers to the product stored correctly in intact packaging. Protect from light. Although the sensitivity of iomeprol to X-rays is low, it is advisable to store the product out of reach of ionizing radiation. Parentized products should be inspected visually for particulate matter and discoloration pror to administration, wherever sublicion and containe premut. Do not use the sublicion if it is discolored to particulate matter and discoloration pror to administration, wherever sublicion and containe premut. Do not use the sublicion is a discolored to particulate matter and discoloration pror to administration or use/handling VI of to tothes containing contrast media sublicion are not interned for the withfravial of multiple doese. The cuber stopper should never be piereed more than once. The use of proper withdrawal cannulae for piercing the stopper and drawing up the contrast medium is recommended. The evolutions is recommended. The contrast medium should not be drawn in the syringe until immediately before use and should not be diluted. Subtisms on used in one examination session or waster materials, such as the connecting tubes, should be disposed. Any residue of contrast medium in the syringe must be discarded. Bottles of 500 mit should be used in conjunction with an injector system. After each patient examination, the connecting tubes to the patient and in drevered to. MARKETING AUTHORISISTION INFORMATION MARKETING AUTHORISISTION INFORMATION
- indentian of the contract of t 8 DATE OF PREPARATION OF THIS DOCUMENT May 2006