HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OMNIPAQUE safely and effectively. See full prescribing information for OMNIPAQUE.

OMNIPAQUE (iohexol) injection, for intrathecal, intravascular, oral, rectal, intraarticular, or body cavity use.
OMNIPAQUE (iohexol) oral solution
Initial U.S. Approval: 1985

WARNING: RISKS WITH INADVERTENT INTRATHECAL ADMINISTRATION OF OMNIPAQUE injection 140 and 350 mg iodine/mL

See full prescribing information for complete boxed warning.

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema (4, 5.1).

----------RECENT MAJOR CHANGES----------

Contraindications (4)	8/2021
Warnings and Precautions (5.9)	2/2022

----------INDICATIONS AND USAGE----------

OMNIPAQUE (iohexol) injection is a radiographic contrast agent indicated for intrathecal, intravascular, oral, rectal, intraarticular and body cavity use. OMNIPAQUE oral solution is indicated for oral use only in conjunction with OMNIPAQUE injection administered intravenously for computed tomography (CT) of the abdomen (1).

----------DOSAGE AND ADMINISTRATION----------

The concentration and volume required will depend on the indication, size and condition of the patient, and the equipment and imaging technique used. For CT of the head and body, OMNIPAQUE may be used with an automated contrast injection system or contrast media management system cleared for use with OMNIPAQUE. See full prescribing information for complete dosing information (2).

----------DOSAGE FORMS AND STRENGTHS----------

OMNIPAQUE Injection

- 140 mg of iodine per mL (302 mg of iohexol/mL) in +*Plus*Pak™ polymer bottles
- 180 mg of iodine per mL (388 mg of iohexol/mL) in glass vials
- 240 mg of iodine per mL (518 mg of iohexol/mL), 300 mg of iodine per mL (647 mg of iohexol/mL) and 350 mg of iodine per mL (755 mg of iohexol/mL) in glass vials and bottles and +*Plus*Pak™ polymer bottles

OMNIPAQUE Oral Solution

- 9 mg of iodine per mL (19 mg of iohexol/mL) and 12 mg of iodine per mL (26 mg of iohexol/mL) in +*Plus*Pak™ polymer bottles

----------CONTRAINDICATIONS----------

- OMNIPAQUE injection 140 and 350 are contraindicated for Intrathecal use (4)
- OMNIPAQUE oral solution 9 and 12 are contraindicated for parenteral use (4)
- OMNIPAQUE body cavity 240 and 300 for hysterosalpingography is contraindicated during pregnancy (or suspected pregnancy), menstruation (or when menstruation is imminent), within 6 months after termination of pregnancy, within 30 days after conization or curettage, when signs of infection are present in any portion of the genital tract, including the external genitalia, and when reproductive tract neoplasia is known or suspected. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Reactions: Life-threatening or fatal reactions can occur. Always have emergency equipment and trained personnel available. (5.3)
- Contrast-Induced Acute Kidney Injury: Acute injury including renal failure can occur. Minimize dose and maintain adequate hydration to minimize risk. (5.4)
- Cardiovascular Adverse Reactions: Hemodynamic disturbances including shock and cardiac arrest may occur during or after administration. (5.5)
- Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age: Monitor these patients for thyroid function abnormalities and treat as clinically needed. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 1.0%) in adult patients after OMNIPAQUE administration. (6.1)

- Intrathecal: Headaches, Pain including backache, neckache, stiffness and neuralgia, nausea, vomiting and dizziness
- Intravascular: Pain, vision abnormalities (including blurred vision and photomas), headache, taste perversion, arrhythmias including premature ventricular contractions (PVCs) and premature atrial contractions (PACs), angina/chest pain, nausea
- Oral: Diarrhea, nausea, vomiting, abdominal pain, flatulence, headache
- Body Cavity: Pain, swelling and heat sensation

Post-marketing adverse reactions (6.2): Hypersensitivity and manifestations like rash, pruritus, urticaria, and dyspnea, in addition chest pain, and swelling.

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: A lactating woman may pump and discard breast milk for 10 hours after OMNIPAQUE administration. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: RISKS WITH INADVERTENT INTRATHECAL ADMINISTRATION
OMNIPAQUE injection, 140 and 350 mg iodine/mL
Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Intrathecal Administration

Adults
OMNIPAQUE 180, 240, and 300
- Myelography (lumbar, thoracic, cervical, total columnar)
- Computerized Tomography (CT) (myelography, cisternography, ventriculography)

Pediatrics
OMNIPAQUE 180
- Myelography (lumbar, thoracic, cervical, total columnar)
- CT (myelography, cisternography)

1.2 Intravascular Administration

Adults
OMNIPAQUE 140
- Intra-arterial digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels

OMNIPAQUE 240
- CT head imaging
- Peripheral venography (phlebography)

OMNIPAQUE 300
- Aortography including studies of the aortic arch, abdominal aorta and its branches
- CT head and body imaging
- Cerebral arteriography
- Peripheral venography (phlebography)
- Peripheral arteriography
- Excretory urography

OMNIPAQUE 350
- Angiocardiography (ventriculography, selective coronary arteriography)
- Aortography including studies of the aortic root, aortic arch, ascending aorta, abdominal aorta and its branches
- CT head and body imaging
- Intravenous digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels
- Peripheral arteriography
- Excretory urography

Pediatrics
OMNIPAQUE 240
- CT head and body imaging

OMNIPAQUE 300
- Angiocardiography (ventriculography)
- Excretory urography
- CT head and body imaging

OMNIPAQUE 350
- Angiocardiography (ventriculography, pulmonary arteriography, venography, and studies of the collateral arteries)
- Aortography including the aortic root, aortic arch, ascending and descending aorta

1.3 Oral or Rectal Administration

Adults
OMNIPAQUE 350
- Oral radiographic examination of the gastrointestinal tract

Pediatrics
OMNIPAQUE 180, 240 and 300
- Oral and rectal radiographic examination of the gastrointestinal tract

1.4 Oral Administration in Conjunction with Intravenous Administration

Diluted OMNIPAQUE Injection

Adults
OMNIPAQUE 240, 300 and 350 diluted and administered orally in conjunction with OMNIPAQUE 300 administered intravenously
- CT of the abdomen

Pediatrics
OMNIPAQUE 240, 300 and 350 diluted and administered orally in conjunction with OMNIPAQUE 240 or OMNIPAQUE 300 administered intravenously
- CT of the abdomen

OMNIPAQUE Oral Solution

Adults
OMNIPAQUE oral solution 9 and 12 administered orally in conjunction with OMNIPAQUE 300 administered intravenously
- CT of the abdomen

Pediatrics
OMNIPAQUE oral solution 9 and 12 administered orally in conjunction with OMNIPAQUE 240 or OMNIPAQUE 300 administered intravenously
- CT of the abdomen

1.5 Intraarticular Administration

Adults
OMNIPAQUE 240, 300, and 350
- Arthrography

1.6 Body Cavity Administration

Adults
OMNIPAQUE 240
- Endoscopic retrograde pancreatography (ERP) and cholangiopancreatography (ERCP)
- Herniography
- Hysterosalpingography

OMNIPAQUE 300
- Hysterosalpingography

Pediatrics
OMNIPAQUE 240, 300 and 350 diluted
- Voiding cystourethrography (VCU)

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- OMNIPAQUE 140, 180, 240, 300 and 350 are indicated for intravascular, oral, rectal, intraarticular, and body cavity administration. OMNIPAQUE 180, 240, and 300 are indicated for intrathecal administration *[see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)]*.
- Use sterile technique for all handling and administration of OMNIPAQUE for intravascular, intrathecal, intraarticular, and body cavity administration.
- OMNIPAQUE oral solution 9 and 12 are indicated for oral use only *[see Contraindications (4) and Warnings and*

Precautions (5.2)].

- Do not use if tamper-evident ring is broken or missing.
- OMNIPAQUE injection may be administered at either body (37°C, 98.6°F) or room temperature (20° to 25°C, 68° to 77°F).
- Inspect OMNIPAQUE injection for particulate matter or discoloration before administration, whenever solution and container permit. Do not administer if OMNIPAQUE injection contains particulate matter or is discolored.
- Do not mix OMNIPAQUE injection with, or inject in intravenous lines containing, other drugs or total nutritional admixtures.
- Use the lowest dose necessary to obtain adequate visualization.
- Individualize the volume, strength, and rate of administration of OMNIPAQUE injection. Consider factors such as age, body weight, vessel size, blood flow rate within the vessel, anticipated pathology, degree and extent of opacification required, structures or area to be examined, disease processes affecting the patient, and equipment and technique to be employed.
- Avoid extravasation when administering OMNIPAQUE injection intravascularly, especially in patients with severe arterial or venous disease *[see Warnings and Precautions (5.6)]*.
- Hydrate patients before and after intravascular administration of OMNIPAQUE injection *[see Warnings and Precautions (5.4)]*.
- Each bottle of OMNIPAQUE injection and oral solution is intended for one procedure only. Discard any unused portion.

2.2 Intrathecal Dosage and Administration

- Rate of injection: Injection should be made slowly over 1 to 2 minutes
- Repeat procedures: If sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body; at least 48 hours should be allowed before repeat examination; however, whenever possible, 5 days to 7 days is recommended.
- If computerized tomographic (CT) myelography follows myelography, delay imaging several hours to allow the degree of contrast to decrease.

TABLE 1 - INTRATHECAL
ADULTS

The usual recommended total doses for use in lumbar, thoracic, cervical, and total columnar myelography in adults are 1,200 mg iodine to 3,100 mg iodine (see below).

STUDY TYPE	INJECTION TYPE	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
LUMBAR MYELOGRAPHY	LUMBAR	OMNIPAQUE 180 OMNIPAQUE 240	10 to 17 7 to 12.5
THORACIC MYELOGRAPHY	LUMBAR CERVICAL	OMNIPAQUE 240 OMNIPAQUE 300	6 to 12.5 6 to 10
CERVICAL MYELOGRAPHY	LUMBAR	OMNIPAQUE 240 OMNIPAQUE 300	6 to 12.5 6 to 10
CERVICAL MYELOGRAPHY	C1-2	OMNIPAQUE 180 OMNIPAQUE 240 OMNIPAQUE 300	7 to 10 6 to 12.5 4 to 10
TOTAL COLUMNAR MYELOGRAPHY	LUMBAR	OMNIPAQUE 240 OMNIPAQUE 300	6 to 12.5 6 to 10

** A total dose of 3,100 mg iodine or a concentration of 300 mg iodine/mL should not be exceeded in adults.*

TABLE 2 – INTRATHECAL PEDIATRICS

The usual recommended total doses for lumbar, thoracic, cervical, and/or total columnar myelography by lumbar puncture in children are 360 mg iodine to 2700 mg iodine (see below). Actual volumes administered depend largely on patient age and the following guidelines are recommended.

AGE	STUDY TYPE	INJECTION TYPE	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
0 up to 3 mos.	LUMBAR, THORACIC, CERVICAL AND/OR TOTAL COLUMNAR MYELOGRAPHY	LUMBAR PUNCTURE	OMNIPAQUE 180	2 to 4
3 up to 36 mos.			OMNIPAQUE 180	4 to 8
3 up to 7 yrs.			OMNIPAQUE 180	5 to 10
7 up to 13 yrs.			OMNIPAQUE 180	5 to 12
13 to 18 yrs.			OMNIPAQUE 180	6 to 15

**A total dose of 2,700 mg iodine or a concentration of 180 mg iodine/mL should not be exceeded in a single myelographic examination in pediatrics.*

2.3 Intravascular Dosage and Administration

Intra-arterial Procedures

TABLE 3 ANGIOCARDIOGRAPHIC PROCEDURES

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 350	VENTRICULOGRAPHY • The recommended single dose is 40 mL (Range of 30 mL to 60 mL) • May be combined with selective coronary arteriography SELECTIVE CORONARY ARTERIOGRAPHY • The recommended single dose is 5 mL (Range of 3 mL to 14 mL) Doses may be repeated as necessary. Maximum volume with multiple injections should not exceed 250 mL.
Pediatrics	OMNIPAQUE 300	VENTRICULOGRAPHY The recommended single dose is 1.75 mL/kg (Range of 1.5 mL/kg to 2 mL/kg) • May be repeated as necessary Maximum dose with multiple injections should not exceed 6 mL/kg up to a total volume of 291 mL.
	OMNIPAQUE 350	VENTRICULOGRAPHY Recommended single dose is 1.25 mL/kg (Range of 1 mL/kg to 1.5 mL/kg). • May be repeated as necessary Maximum dose with multiple injections should not exceed 5 mL/kg up to a total volume of 250 mL. PULMONARY ANGIOGRAPHY (PULMONARY ARTERIOGRAPHY AND/OR PULMONARY VENOGRAPHY) The recommended single dose is 1 mL/kg.

TABLE 4
AORTOGRAPHY

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 300 and 350	AORTOGRAPHY AND SELECTIVE VISCERAL ARTERIOGRAPHY The recommended single dose is: • 50 mL to 80 mL for the aorta (aortic arch, ascending aorta) • 30 mL to 60 mL for abdominal aorta and its branches (celiac, mesenteric, hepatic and splenic arteries) • 5 mL to 15 mL for renal arteries Injections may be repeated if indicated, but the total volume should not exceed: • 290 mL of OMNIPAQUE 300 • 250 mL of OMNIPAQUE 350
	OMNIPAQUE 350	AORTIC ROOT AND ARCH STUDY WHEN USED ALONE The recommended single dose is 50 mL (Range of 20 mL to 75 mL)
Pediatrics	OMNIPAQUE 350	AORTOGRAPHY (AORTIC ROOT, AORTIC ARCH, AND DESCENDING AORTA) The recommended single dose is 1 mL/kg. • May be repeated as necessary Maximum dose should not exceed 5 mL/kg up to a total volume of 250 mL.

TABLE 5
CEREBRAL ARTERIOGRAPHY

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 300	Single dose for cerebral arteriography is as follows: • Common carotid artery (6 mL to 12 mL) • Internal carotid artery (8 mL to 10 mL) • External carotid artery (6 mL to 9 mL) • Vertebral artery (6 mL to 10 mL)

TABLE 6
INTRA-ARTERIAL DIGITAL SUBTRACTION ANGIOGRAPHY

HEAD, NECK, ABDOMINAL, RENAL AND PERIPHERAL VESSELS

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)		
		ARTERIES	VOLUME/INJECTION (mL)	RATE OF INJECTION (mL/sec)
Adults	OMNIPAQUE 140	Aorta	20 to 45	8 to 20
		Carotid	5 to 10	3 to 6
		Femoral	9 to 20	3 to 6
		Vertebral	4 to 10	2 to 8
		Renal	6 to 12	3 to 6
		Other branches of aorta (includes subclavian, axillary, innominate and iliac)	8 to 25	3 to 10

Mechanical or hand injection can be used to administer one or more bolus intra-arterial injections of OMNIPAQUE 140.

TABLE 7
PERIPHERAL ARTERIOGRAPHY

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 300 and 350	The recommended dose for use in peripheral angiography is as follows: Aortofemoral runoffs: • 30 mL to 90 mL of OMNIPAQUE 300 • 20 mL to 70 mL of OMNIPAQUE 350 Selective arteriograms: • 10 mL to 60 mL of OMNIPAQUE 300 • 10 mL to 30 mL of OMNIPAQUE 350

Intravenous Procedures

TABLE 8
PERIPHERAL VENOGRAPHY
(PHLEBOGRAPHY)

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 240 and 300	The recommended dose (per leg) is: • 20 mL to 150 mL of OMNIPAQUE 240 • 40 mL to 100 mL of OMNIPAQUE 300

TABLE 9
EXCRETORY UROGRAPHY

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Adults	OMNIPAQUE 300 and 350	The recommended dose is: • 0.6 mL/kg to 1.2 mL/kg body weight
Pediatrics	OMNIPAQUE 300	Dose ranging from 0.5 mL/kg to 3 mL/kg of body weight: • The usual dose for children is 1 mL/kg to 1.5 mL/kg. • The total administered dose should not exceed 3 mL/kg.

TABLE 10
DIGITAL SUBTRACTION ANGIOGRAPHY
HEAD, NECK, ABDOMINAL, RENAL AND PERIPHERAL VESSELS

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)	RATE OF INJECTION (mL/sec)
Adults	OMNIPAQUE 350	The usual dose for the intravenous digital technique is 30 mL to 50 mL. Frequently three or more doses may be required, up to a total volume not to exceed 250 mL	7.5 mL/second to 30 mL/second using a pressure injector

TABLE 11
CT SCANNING OF THE HEAD AND BODY

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME* (mL)
Adults	OMNIPAQUE 240, 300 and 350	Head and body imaging by rapid injection **CT Imaging – Head:** • 70 mL to 150 mL of OMNIPAQUE 300 • 80 mL of OMNIPAQUE 350 **CT Imaging – Body:** • 50 mL to 200 mL of OMNIPAQUE 300 • 60 mL to 100 mL of OMNIPAQUE 350 Head imaging by infusion **CT Imaging – Head:** • 120 mL to 250 mL of OMNIPAQUE 240
Pediatrics	OMNIPAQUE 240 and 300	**CT Imaging – Head and Body:** • 1 mL/kg to 2 mL/kg (with maximum = 3 mL/kg) • Maximum single dose = 116 mL

**OMNIPAQUE may be used with an automated contrast injection system or contrast management system cleared for use with OMNIPAQUE [see Dosage and Administration (2.8)]. See device labeling for device indications, additional information, and instructions for use.*

2.4 Oral or Rectal Dosage and Administration

Oral and Rectal Administration – Undiluted OMNIPAQUE Injection for Radiographic Examination of the Gastrointestinal (GI) Tract

TABLE 12
DOSING FOR RADIOGRAPHIC EXAMINATION OF THE GI TRACT

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	ORAL VOLUME (mL)	RECTAL VOLUME* (mL)
Adults	OMNIPAQUE 350	The recommended dose is 50 mL to 100 mL	-
Pediatrics	OMNIPAQUE 180, 240 and 300	The recommended dose is 5 mL to 100 mL	The recommended dose is 5 mL to 100 mL*
Less than 3 months old	OMNIPAQUE 180	5 mL to 30 mL	-*
Three months to 3 years	OMNIPAQUE 180, 240 and 300	Up to 60 mL	-*
Four years to 10 years	OMNIPAQUE 180, 240 and 300	Up to 80 mL	-*
Greater than 10 years		Up to 100 mL	-*

**When given rectally, larger volumes may be used.*

2.5 Oral Dosage and Administration in Conjunction with Intravenous Administration

See Table 16 for concurrent intravenous dosing.

Oral Administration of Diluted OMNIPAQUE Injection in Conjunction with Intravenous Administration of OMNIPAQUE Injection for CT of the Abdomen

TABLE 13
DOSING OF DILUTED* OMNIPAQUE INJECTION FOR ORAL ADMINISTRATION

PATIENT POPULATION	ORAL CONCENTRATION (mg iodine/mL)	ORAL VOLUME (mL)	ADMINISTRATION INSTRUCTIONS
Adults	OMNIPAQUE 240, 300 and 350 DILUTED to 6 to 12 mg iodine/mL *(See Table 14 below)*	Recommended oral dose is: • 500 mL to 1,000 mL	Smaller administered volumes can be given if the iodine concentration in final diluted product is increased *(See Table 14 below)* The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.
Pediatrics	OMNIPAQUE 240, 300 and 350 DILUTED to 9 to 21 mg iodine/mL *(See Table 14 below)*	Recommended oral dose is: • 180 mL to 750 mL Do not exceed an oral dose of 5 grams iodine for patients less than 3 years old. Do not exceed an oral dose of 10 grams iodine for patients 3 to 18 years old.	Smaller administered volumes can be given if the iodine concentration in final diluted product is increased *(See Table 14 below)* The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.

**Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.*

TABLE 14
PROCEDURE FOR PREPARATION OF DILUTED OMNIPAQUE INJECTION FOR ORAL ADMINISTRATION

OMNIPAQUE to be mixed with liquid such as water, carbonated beverage, milk, infant formula, or juice to achieve one liter of oral contrast agent.

Final Iodine Concentration of Diluted Contrast Agent (mg iodine/mL)	OMNIPAQUE 240		OMNIPAQUE 300		OMNIPAQUE 350	
	Volume of Contrast Agent (mL)	Volume of Liquid (mL)	Volume of Contrast Agent (mL)	Volume of Liquid (mL)	Volume of Contrast Agent (mL)	Volume of Liquid (mL)
6	25	975	20	980	17	983
9	38	962	30	970	26	974
12	50	950	40	960	35	965
15	63	937	50	950	43	957
18	75	925	60	940	52	948
21	88	912	70	930	60	940

Oral Administration of OMNIPAQUE Oral Solution in Conjunction with Intravenous Administration of OMNIPAQUE Injection for CT of the Abdomen

TABLE 15
DOSING AND ADMINISTRATION OF OMNIPAQUE ORAL SOLUTION

PATIENT POPULATION	ORAL CONCENTRATION (mg iodine/mL)	ORAL VOLUME (mL)	ADMINISTRATION INSTRUCTIONS
Adults	OMNIPAQUE oral solution 9 and 12	The recommended oral dose is: • 500 mL to 1,000 mL	The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.
Pediatrics	OMNIPAQUE oral solution 9 and 12	The recommended oral dose is: • 180 mL to 750 mL Do not exceed an oral dose of 5 grams iodine for patients less than 3 years old. Do not exceed an oral dose of 10 grams iodine for patients 3 to 18 years old.	The oral dosage may be given all at once or over a period of up to 45 minutes if there is difficulty in consuming the required volume.

TABLE 16
INTRAVENOUS ADMINISTRATION OF OMNIPAQUE INJECTION FOR CT OF THE ABDOMEN IN CONJUNCTION WITH ORALLY ADMINISTERED DILUTED OMNIPAQUE INJECTION OR OMNIPAQUE ORAL SOLUTION

PATIENT POPULATION	INTRAVENOUS CONCENTRATION (mg iodine/mL)	INTRAVENOUS VOLUME* (mL)	ADMINISTRATION INSTRUCTIONS
Adults	OMNIPAQUE 300	The recommended dose is: • 100 mL to 150 mL	Administer up to 40 minutes AFTER consumption of the oral dose
Pediatrics	OMNIPAQUE 240 and 300	The recommended dose is: • 2 mL/kg with a range of 1 mL/kg to 2 mL/kg (maximum 3 mL/kg)	Administer up to 60 minutes AFTER consumption of the oral dose

**OMNIPAQUE may be used with an automated contrast injection system or contrast management system cleared for use with OMNIPAQUE [see Dosage and Administration (2.8)]. See device labeling for device indications, additional information, and instructions for use.*

2.6 Intraarticular Dosage and Administration

TABLE 17 ARTHROGRAPHY				
PATIENT POPULATION	**LOCATION**	**CONCENTRATION (mg iodine/mL)**	**VOLUME (mL)**	**DOUBLE CONTRAST/ SINGLE CONTRAST**
Adults	Knee*	OMNIPAQUE 240	5 to 15	Lower volumes recommended for double-contrast examinations; higher volumes recommended for single-contrast examinations.
		OMNIPAQUE 300	5 to 15	
		OMNIPAQUE 350	5 to 10	
Adults	Shoulder*	OMNIPAQUE 240	3	
		OMNIPAQUE 300	10	
Adults	Temporomandibular*	OMNIPAQUE 300	0.5 to 1	
**Passive or active manipulation is used to disperse the medium throughout the joint space.*				

2.7 Body Cavity Dosage and Administration

Body Cavity Administration - Undiluted OMNIPAQUE Injection

TABLE 18 ENDOSCOPIC RETROGRADE PANCREATOGRAPHY (ERP) ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ECRP)		
PATIENT POPULATION	**CONCENTRATION (mg iodine/mL)**	**VOLUME (mL)**
Adults	OMNIPAQUE 240	10 mL to 50 mL but may vary depending on individual anatomy and/or disease state.

TABLE 19 HYSTEROSALPINGOGRAPHY		
PATIENT POPULATION	**CONCENTRATION (mg iodine/mL)**	**VOLUME (mL)**
Adults	OMNIPAQUE 240 and 300	15 mL to 20 mL but may vary depending on individual anatomy and/or disease state.

TABLE 20 HERNIOGRAPHY		
PATIENT POPULATION	**CONCENTRATION (mg iodine/mL)**	**VOLUME (mL)**
Adults	OMNIPAQUE 240	50 mL but may vary depending on individual anatomy and/or disease state.

Body Cavity Administration - Diluted OMNIPAQUE Injection

TABLE 21
VOIDING CYSTOURETHROGRAPHY (VCU)
(CAN BE PERFORMED IN CONJUNCTION WITH EXCRETORY UROGRAPHY)

PATIENT POPULATION	CONCENTRATION (mg iodine/mL)	VOLUME (mL)
Pediatrics	The concentration may vary depending upon the patient's size and age and with the technique and equipment used. OMNIPAQUE injection may be diluted with Sterile Water for Injection. *(See Table 22 below).*	OMNIPAQUE injection may be diluted, utilizing aseptic technique, with Sterile Water for Injection to a concentration of 50 mg iodine/mL to 100 mg iodine/mL for voiding cystourethrography. Range: • 50 mL to 300 mL of DILUTED OMNIPAQUE at a concentration of 100 mg iodine/mL • 50 mL to 600 mL of DILUTED OMNIPAQUE at a concentration of 50 mg iodine/mL.

TABLE 22
PROCEDURE FOR PREPARATION OF DILUTED* OMNIPAQUE INJECTION FOR VCU

Final Iodine Concentration of Diluted Contrast Agent (mg iodine/mL)	Volume of OMNIPAQUE 240 (mL)	Volume of Sterile Water for Injection (mL)	Volume of OMNIPAQUE 300 (mL)	Volume of Sterile Water for Injection (mL)	Volume of OMNIPAQUE 350 (mL)	Volume of Sterile Water for Injection (mL)
100	100	140	100	200	100	250
90		167		233		289
80		200		275		338
70		243		330		400
60		300		400		483
50		380		500		600

**Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.*

2.8 Instructions for Use with an Automated Contrast Injection System or Contrast Management System for CT of the Head and Body

- OMNIPAQUE may be used with an automated contrast injection system cleared for use with contrast media.
  - See above Important Dosage and Administration Instructions for OMNIPAQUE (2.1).
  - See device labeling for information on device indications, instructions for use, and techniques to help assure safe use.
- OMNIPAQUE 300 mg iodine/mL and 350 mg iodine/mL in 150 mL bottles may be used with a contrast media management system cleared for use with OMNIPAQUE 300 mg iodine/mL and 350 mg iodine/mL in 150 mL bottles.
  - See device labeling for information on device indications, instructions for use, and techniques to help assure safe use.
  - Use sterile technique for penetrating the container closure of OMNIPAQUE 300 and 350 and transferring OMNIPAQUE solution. The container closure may be penetrated only one time with a suitable sterile component of the contrast media management system cleared for use with OMNIPAQUE 300 and 350 in 150 mL bottles.
  - Once the OMNIPAQUE 300 and 350 Injection is punctured, do not remove the bottle from the work area during the entire period of use.
  - Maximum use time is 4 hours after initial puncture.
  - Each bottle is for one procedure only. Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

OMNIPAQUE (iohexol) Injection and Oral Solution
Sterile, pyrogen-free, gluten-free, colorless to pale yellow solution containing the nonionic, water-soluble x-ray contrast medium iohexol, and available in the following strengths and formats:

OMNIPAQUE (iohexol) Injection

- 140 mg of organically bound iodine per mL (302 mg iohexol/mL)
  - Available in +*PLUS*PAK™ (polymer bottle)
- 180 mg of organically bound iodine per mL (388 mg iohexol/mL)
  - Available in glass vials
- 240 mg of organically bound iodine per mL (518 mg iohexol/mL)
- 300 mg of organically bound iodine per mL (647 mg iohexol/mL)
- 350 mg of organically bound iodine per mL (755 mg iohexol/mL)
  - Available in glass vials and bottles and +*PLUS*PAK™ polymer bottles.

OMNIPAQUE Oral Solution

- 9 mg of organically bound iodine per mL (19 mg iohexol/mL)
- 12 mg of organically bound iodine per mL (26 mg iohexol/mL)
  - Available in +*PLUS*PAK™ polymer bottles.

4 CONTRAINDICATIONS

- OMNIPAQUE 140 and OMNIPAQUE 350 are contraindicated for intrathecal use *[see Warnings and Precautions (5.1)]*
- OMNIPAQUE oral solution 9 and 12 are contraindicated for parenteral administration *[see Warnings and Precautions (5.2)]*
- OMNIPAQUE body cavity 240 and 300 for hysterosalpingography is contraindicated during pregnancy or suspected pregnancy, menstruation or when menstruation is imminent, within 6 months after termination of pregnancy, within 30 days after conization or curettage, when signs of infection are present in any portion of the genital tract including the external genitalia, and when reproductive tract neoplasia is known or suspected because of the risk of peritoneal spread of neoplasm.

5 WARNINGS AND PRECAUTIONS

5.1 Risks Associated with Inadvertent Intrathecal Administration

OMNIPAQUE injection 140 and 350 are contraindicated for intrathecal use *[see Contraindications (4) and Dosage and Administration (2.1)]*. Inadvertent intrathecal administration can cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

5.2 Risks Associated with Inadvertent Parenteral Administration

OMNIPAQUE oral solution 9 and 12 are contraindicated for parenteral administration *[see Contraindications (4) and Dosage and Administration (2.1)]*. Adverse reactions such as hemolysis may occur if administered intravascularly. Do not administer OMNIPAQUE oral solution 9 and 12 parenterally.

5.3 Hypersensitivity Reactions

OMNIPAQUE can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Most severe reactions develop shortly after the start of the injection (within 3 minutes), but reactions can occur up to hours later. There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (i.e., bronchial asthma, drug, or food allergies) or other hypersensitivities. Premedication with antihistamines or corticosteroids does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

Obtain a history of allergy, hypersensitivity, or hypersensitivity reactions to iodinated contrast agents and always have emergency resuscitation equipment and trained personnel available prior to OMNIPAQUE administration. Monitor all patients for hypersensitivity reactions.

5.4 Contrast-Induced Acute Kidney Injury

Acute kidney injury, including renal failure, may occur after parenteral administration of OMNIPAQUE. Risk factors include: pre-existing renal impairment, dehydration, diabetes mellitus, congestive heart failure, advanced vascular disease, elderly age, concomitant use of nephrotoxic or diuretic medications, multiple myeloma/paraproteinaceous diseases, repetitive and/or large doses of an iodinated contrast agent.

Use the lowest necessary dose of OMNIPAQUE in patients with renal impairment. Adequately hydrate patients prior to and following parenteral administration of OMNIPAQUE. Do not use laxatives, diuretics, or preparatory dehydration prior to OMNIPAQUE administration.

5.5 Cardiovascular Adverse Reactions

Life-threatening or fatal cardiovascular reactions including hypotension, shock, cardiac arrest have occurred with the parenteral administration of OMNIPAQUE. Most deaths occur during injection or five to ten minutes later, with cardiovascular disease as the main aggravating factor. Cardiac decompensation, serious arrhythmias, and myocardial ischemia or infarction can occur during coronary arteriography and ventriculography.

Based upon clinical literature reported deaths from the administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%). Use the lowest necessary dose of OMNIPAQUE in patients with congestive heart failure and always have emergency resuscitation equipment and trained personnel available. Monitor all patients for severe cardiovascular reactions.

5.6 Thromboembolic Events

Angiocardiography

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke can occur during angiocardiography procedures with both ionic and nonionic contrast media. During these procedures, increased thrombosis and activation of the complement system occurs. Risk factors for thromboembolic events include: length of procedure, catheter and syringe material, underlying disease state, and concomitant medications.

To minimize thromboembolic events, use meticulous angiographic techniques, and minimize the length of the procedure. Avoid blood remaining in contact with syringes containing iodinated contrast agents, which increases the risk of clotting. Avoid angiocardiography in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

5.7 Extravasation and Injection Site Reactions

Extravasation of OMNIPAQUE during intravascular injection may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease. Ensure intravascular placement of catheters prior to injection. Monitor patients for extravasation and advise patients to seek medical care for progression of symptoms.

5.8 Thyroid Storm in Patients with Hyperthyroidism

Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule. Evaluate the risk in such patients before use of OMNIPAQUE.

5.9 Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age

Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media. Among patients 0 to 3 years of age exposed to iodinated contrast media, thyroid dysfunction has been reported in 1% to 15% depending on the age of the patient and the dose of the iodinated contrast agent.

Younger age, very low birth weight, prematurity, and the presence of other conditions, such as, admission to neonatal or pediatric intensive care units, and cardiac conditions are associated with an increased risk. Pediatric patients with cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures, such as catheterization and computed tomography (CT).

Pediatric patients 0 to 3 years of age warrant closer monitoring because an underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. Evaluate thyroid function in all pediatric patients 0 to 3 years of age within 3 weeks following exposure to iodinated contrast media, especially in term and preterm neonates. If thyroid dysfunction is detected, treat and monitor thyroid function as clinically needed.

5.10 Hypertensive Crisis in Patients with Pheochromocytoma

Hypertensive crisis has occurred after the use of iodinated contrast agents in patient with pheochromocytoma. Monitor patients when administering OMNIPAQUE intravascularly if pheochromocytoma or catecholamine-secreting paragangliomas are suspected. Inject the minimum amount of contrast necessary, assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.

5.11 Sickle Cell Crisis in Patients with Sickle Cell Disease

Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease. Hydrate patients prior to and following OMNIPAQUE administration and use OMNIPAQUE only if the necessary imaging information cannot be obtained with alternative imaging modalities.

5.12 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agents; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering OMNIPAQUE to patients with a history of a severe cutaneous adverse reaction to OMNIPAQUE.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks Associated with Inadvertent Intrathecal Administration *[see Warnings and Precautions (5.1)]*
- Risks Associated with Inadvertent Parenteral Administration *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Contrast-Induced Kidney Injury *[see Warnings and Precautions (5.4)]*
- Cardiovascular Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Thromboembolic Events *[see Warnings and Precautions (5.6)]*
- Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age *[see Warnings and Precautions (5.9)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Intrathecal Administration

Adults

TABLE 23
ADVERSE REACTIONS – INTRATHECAL ADMINISTRATION

In controlled clinical studies involving 1531 patients using OMNIPAQUE the following adverse reactions were reported:

System Organ Class	Adverse Reaction	Incidence
Nervous System	Headaches	18%
Musculoskeletal and Connective Tissue	Pain including backache, neckache, stiffness and neuralgia	8%
Gastrointestinal System	Nausea	6%
	Vomiting	3%
Nervous System	Dizziness	2%
Other Reactions	Feeling of heaviness, hypotension, hypertonia, sensation of heat, sweating, vertigo, loss of appetite, drowsiness, hypertension, photophobia, tinnitus, neuralgia, paresthesia, difficulty in micturition, and neurological changes	<0.1%

Pediatric Patients

TABLE 24
ADVERSE REACTIONS – INTRATHECAL ADMINISTRATION

In clinical studies involving 152 patients for pediatric myelography by lumbar puncture, adverse events following the use of OMNIPAQUE 180 were generally similar to those reported in adults.

Procedure	System Organ Class	Adverse Reaction	Incidence
Myelography by Lumbar Puncture	Nervous System	Headache	9%
	Gastrointestinal System	Vomiting	6%
	Musculoskeletal and Connective Tissue	Backache	1.3%
	Other Reactions *All were transient and mild with no clinical sequelae.*	Fever	<0.7%
		Hives	
		Stomachache	
		Visual Hallucination	

		Neurological Changes	

Intravascular Administration

Immediately following intravascular injection of contrast medium, a transient sensation of mild warmth is not unusual. Warmth is less frequent with OMNIPAQUE than with ionic contrast media.

Adults

In controlled clinical studies involving 1485 patients, the following adverse reactions occurred (Table 25).

TABLE 25
ADVERSE REACTIONS – INTRAVASCULAR ADMINISTRATION

System Organ Class	Adverse Reaction	Incidence
Cardiovascular System	Arrhythmias including PVCs and PACs	2%
	Hypotension	0.7%
	Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction	≤ 0.3%
Nervous System	Vertigo (including dizziness and lightheadedness)	0.5%
	Pain	3%
	Vision Abnormalities (including blurred vision and photomas)	2%
	Taste Perversion	1%
Other Reactions	Anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus	Individual incidence of 0.3% or less
Respiratory System	Dyspnea, rhinitis, coughing, and laryngitis	Individual incidence of 0.2% or less
Gastrointestinal System	Nausea	2%
	Vomiting	0.7%
	Others including diarrhea, dyspepsia, cramp, and dry mouth	Individual incidence of less than 0.1%.
Skin and Subcutaneous Tissues	Urticaria	0.3%
	Purpura	0.1%
	Abscess	0.1%
	Pruritus	0.1%

Pediatric Patients

In controlled clinical studies involving 391 patients for pediatric angiocardiography, urography, and CT head imaging, adverse reactions following the use of OMNIPAQUE 240, 300, and 350 were generally similar in quality and frequency to those reported in adults (Table 26).

TABLE 26
ADVERSE REACTIONS – INTRAVASCULAR ADMINISTRATION

System Organ Class	Adverse Reaction	Incidence
Cardiovascular System	Ventricular Tachycardia	0.5%
	2:1 Heart Block	0.5%
	Hypertension	0.3%
	Anemia	0.3%
General Disorders and Administration Site Conditions	Pain	0.8%
	Fever	0.5%
Nervous System	Convulsion	0.3%
	Taste Abnormality	0.5%
Respiratory System	Congestion	0.3%
	Apnea	0.3%
Gastrointestinal System	Nausea	1%
	Vomiting	2%
Endocrine System	Hypoglycemia	0.3%
Skin and Subcutaneous Tissue	Rash	0.3%

Oral Administration for Examination of the Gastrointestinal Tract

Adults
Nausea, vomiting, and diarrhea have been most frequently reported following orally administered undiluted OMNIPAQUE for radiographic examination of the gastrointestinal tract. In controlled clinical studies involving 54 adult patients for oral radiographic examination of the gastrointestinal tract using undiluted OMNIPAQUE 350 the following adverse reactions were reported (Table 27).

TABLE 27
ADVERSE REACTIONS – ORAL ADMINISTRATION OF UNDILUTED OMNIPAQUE 350

System Organ Class	Adverse Reaction	Incidence
Gastrointestinal System	Diarrhea	42%
	Nausea	15%
	Vomiting	11%
	Abdominal Pain	7%
	Flatulence	2%
Nervous System	Headache	2%

Pediatrics Patients (Oral and Rectal Administration)
In clinical studies involving 58 pediatric patients, the adverse reactions were found to mostly affect the gastrointestinal system with diarrhea (36%), vomiting (9%), nausea (5%) and abdominal pain (2%). However, fever (5%), hypotension (2%) and urticaria (2%) were also reported.

Oral Administration for CT of the Abdomen in Conjunction with Intravenous Administration

Adults
In a controlled clinical study involving 44 adult patients receiving oral administration of diluted OMNIPAQUE (4-9 mg iodine/mL) in conjunction with intravenously injected OMNIPAQUE 300 for CT examination of the abdomen, adverse reactions were limited to a single report of vomiting.

Pediatric Patients
In clinical studies involving 69 pediatric patients receiving oral administration of diluted OMNIPAQUE (9-29 mg iodine/mL) in conjunction with intravenously administered OMNIPAQUE 240 and OMNIPAQUE 300 for CT examination of the abdomen, adverse reactions were limited to a single report of vomiting (1.4%).

Body Cavity Use

Adults
Arthrography: In controlled clinical studies involving 285 adult patients for various body cavity examinations using OMNIPAQUE 240, 300 and 350, the most frequent adverse reactions were administration site reactions: pain 26% and swelling 22%, were exclusively reported for arthrography and were generally related to the procedure rather than the contrast medium. Patients also experienced heat (7%). All other adverse reaction occurred at a rate less than or equal to 1%.

Pediatric Patients
No adverse reactions associated with the use of OMNIPAQUE for VCU procedures were reported in 51 pediatric patients studied.

6.2 Post-marketing Experience

The following additional reactions listed by indication have been identified during post-approval use of OMNIPAQUE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General

Immune System Disorders: Hypersensitivity reactions, anaphylactic or anaphylactoid reactions, anaphylactic or anaphylactoid shock including life-threatening or fatal anaphylaxis

General Disorders and Administration Site Conditions: Pyrexia, chills, pain and discomfort, asthenia, administration site conditions including extravasation

Intrathecal Administration

Nervous System Disorders: Meningism, aseptic meningitis, seizures or status epilepticus, disorientation, coma, depressed or loss of consciousness, transient contrast-induced toxic encephalopathy (including amnesia, hallucination, paralysis, paresis, speech disorder, aphasia, dysarthria), restlessness, tremors, hypoesthesia

Musculoskeletal and Connective Tissue Disorders: Pain, muscle spasms or spasticity

Psychiatric Disorders: Confusional state, agitation, anxiety

Eye Disorders: Transient visual impairment including cortical blindness

Renal Reactions: Acute kidney injury

Intravascular Administration

Cardiovascular Disorders: Severe cardiac complications (including cardiac arrest, cardiopulmonary arrest), shock, peripheral vasodilatation, palpitations, vasospasm including spasm of coronary arteries, myocardial infarction, syncope, cyanosis, pallor, flushing, chest pain

Hemodynamic Reactions: Vasospasm and thrombophlebitis following intravenous injection

Blood and Lymphatic System Disorders: Neutropenia

Nervous System Disorders: Disorientation, coma, depressed or loss of consciousness, transient contrast-induced toxic encephalopathy (including amnesia, hallucination, paralysis, paresis, speech disorder, aphasia, dysarthria), restlessness, tremors, hypoesthesia

Psychiatric Disorders: Confusional state, agitation

Eye Disorders: Eye irritation or itchiness, periorbital edema, ocular or conjunctival hyperemia, lacrimation

Renal Reactions: Acute kidney injury, toxic nephropathy (CIN), transient proteinuria, oliguria or anuria, increased serum creatinine

Gastrointestinal Disorders: Abdominal pain, pancreatitis aggravated, salivary gland enlargement

Endocrine Reactions: Hyperthyroidism, hypothyroidism

Respiratory; Thoracic, and Mediastinal Disorders: Respiratory distress, respiratory failure, pulmonary edema, bronchospasm, laryngospasm, throat irritation, throat tightness, laryngeal edema, wheezing, chest discomfort, asthmatic attack

Skin and Subcutaneous Tissue Disorders: Contrast media reactions range from mild (e.g., pleomorphic rashes, drug eruption, erythema and skin discoloration, blisters, hyperhidrosis, angioedema, localized areas of edema) to severe: [e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), bullous or exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)]

Oral Administration

Gastrointestinal Disorders: Dysphagia, abdominal pain

Body Cavity Administration

Gastrointestinal Disorders: Pancreatitis

Musculoskeletal and Connective Tissue Disorders: Arthritis (arthrography)

Hysterosalpingography: Injection of OMNIPAQUE for hysterosalpingography is associated with immediate, transient pain. Monitor injection pressure and volume instilled to minimize pain and to avoid disruptive distention of the uterus and fallopian tubes. Fluoroscopic monitoring is recommended.

Nervous system: Pain (49%), somnolence and fever each with an individual incidence of 3%

Gastrointestinal system: Nausea (3%)

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

Metformin

In patients with renal impairment, metformin can cause lactic acidosis. Iodinated contrast agents appear to increase the risk of metformin-induced lactic acidosis, possibly as a result of worsening renal function. Stop metformin at the time of, or prior to, OMNIPAQUE administration in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48

hours after the imaging procedure, and reinstitute metformin only after renal function is stable.

Radioactive Iodine
Administration of iodinated contrast agents may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy in patients with carcinoma of the thyroid. The decrease in efficacy lasts for 6 to 8 weeks.

Beta-adrenergic Blocking Agents
The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and reduces the responsiveness of treatment of hypersensitivity reactions with epinephrine. Because of the risk of hypersensitivity reactions, use caution when administering OMNIPAQUE to patients taking beta-blockers.

Drugs that Lower Seizure Threshold
Drugs that lower seizure threshold, especially phenothiazine derivatives including those used for their antihistaminic or antinauseant properties, are not recommended for use with intrathecal administration of OMNIPAQUE.

CNS Active Drugs
Drugs such as monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. Such medications should be discontinued at least 48 hours before myelography, should not be used for the control of nausea or vomiting during or after myelography, and should not be resumed for at least 24 hours post procedure. In non-elective procedures in patients on these drugs, consider prophylactic use of anticonvulsants.

7.2 Drug-Laboratory Test Interactions

Effect on Thyroid Tests
If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests that do not depend on iodine estimation, e.g., T_3 resin uptake or direct thyroxine assays, are not affected.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Hysterosalpingography is contraindicated in pregnant women due to the potential risk to the fetus from an intrauterine procedure *[see Contraindications (4)]*. There are no data with iohexol use in pregnant women to inform any drug-associated risks. Iohexol crosses the placenta and reaches fetal tissues in small amounts *(*see *Data)*. In animal reproduction studies, no developmental toxicity occurred with intravenous iohexol administration to rats and rabbits at doses up to 0.4 (rat) and 0.5 (rabbit) times the maximum recommended human intravenous dose (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Literature reports show that intravenously administered iohexol crosses the placenta and is visualized in the digestive tract of exposed infants after birth.

Animal Data

Iohexol was neither embryotoxic nor teratogenic in either rats or rabbits at the following dose levels tested: 1.0, 2.0, 4.0 g iodine/kg in rats, administered intravenously to 3 groups of 25 dams once daily during days 6 through 15 of pregnancy; 0.3, 1.0, 2.5 g iodine/kg in rabbits, administered intravenously to 3 groups of 18 rabbits dosed once a day during days 6 through 18 of pregnancy.

8.2 Lactation

Risk Summary

Published literature reports that breast feeding after intravenous iohexol administration to the mother would result in the infant receiving an oral dose of approximately 0.7% of the maternal intravenous dose; however, lactation studies have not been conducted with oral, intrathecal, or intracavity administration of iohexol. There is no information on the effects of the drug on the breastfed infant or on milk production. Iodinated contrast agents are excreted unchanged in human milk in very low amounts with poor absorption from the gastrointestinal tract of a breastfed infant. Exposure to iohexol to a breastfed infant can be minimized by temporary discontinuation of breastfeeding (see Clinical Considerations). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OMNIPAQUE and any potential adverse effects on the breastfed infant from OMNIPAQUE or from the underlying maternal condition.

Clinical Considerations

Interruption of breastfeeding after exposure to iodinated contrast agents is not necessary because the potential exposure of the breastfed infant to iodine is small. However, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 elimination half-lives) after OMNIPAQUE administration to minimize drug exposure to a breastfed infant.

8.4 Pediatric Use

Intrathecal Use

The safety and effectiveness of OMNIPAQUE 180 have been established in pediatric patients 2 weeks to 17 years of age for myelography (lumbar, thoracic, cervical, total columnar) and for CT (myelography, cisternography). Use of OMNIPAQUE 180 is supported by controlled clinical studies in adults for myelography, in addition to clinical studies in pediatric patients undergoing myelography. The safety and effectiveness of OMNIPAQUE 180 have not been established for intrathecal use in patient pediatric patients less than 2 weeks of age. The safety and effectiveness of OMNIPAQUE 240 and 300 have not been established in pediatric patients for myelography (lumbar, thoracic, cervical, total columnar) and for CT (myelography, cisternography, or ventriculography).

Intravascular Use

Angiocardiography (*Ventriculography, Pulmonary Arteriography, Venography, and Studies of the Collateral Arteries) and Aortography*

The safety and effectiveness of OMNIPAQUE 300 have been established in pediatric patients from birth to 17 years of age for angiocardiography (ventriculography) and of OMNIPAQUE 350 in pediatric patients from birth to 17 years of age for angiocardiography (ventriculography, pulmonary arteriography, venography, and studies of the collateral arteries) and aortography. Use of OMNIPAQUE 300 and 350 is supported by controlled clinical studies in adults for angiocardiography and aortography, in addition to controlled clinical studies in pediatric patients undergoing angiocardiography, including aortography. The safety and effectiveness of OMNIPAQUE 300 have not been established in pediatric patients for aortography.

Intra-arterial Digital Subtraction Angiography, Intravenous Digital Subtraction Angiography, Cerebral Arteriography, or Peripheral Arteriography and Venography

The safety and effectiveness of OMNIPAQUE have not been established in pediatric patients for intra-arterial digital subtraction angiography, intravenous digital subtraction angiography, cerebral arteriography, or peripheral arteriography and venography.

CT of the Head and Body

The safety and effectiveness of OMNIPAQUE 240 and 300 have been established in pediatric patients from birth to 17 years of age for CT imaging of the head and body. Use of OMNIPAQUE 240 and 300 is supported by controlled clinical studies in adults for head and body CT, in addition to clinical studies in pediatric patients undergoing head CT and in 69 pediatric patients undergoing CT of the abdomen after oral administration of diluted OMNIPAQUE plus intravenous administration of OMNIPAQUE. The safety and effectiveness of OMNIPAQUE 350 have not been established in pediatric patients for CT imaging of the head and body.

Urography

The safety and effectiveness of OMNIPQUE 300 have been established in pediatric patients from birth to 17 years of age for urography. Use of OMNIPAQUE 300 is supported by controlled clinical studies in adults for urography, in addition to controlled clinical studies in pediatric patients undergoing urography and clinical safety data in pediatric patients down to birth.

Oral or Rectal Use

Undiluted OMNIPAQUE Injection

The safety and effectiveness of OMNIPAQUE 180, 240, and 300 administered orally and rectally have been established in pediatric patients, from birth to 17 years of age for examination of the GI tract. Use of OMNIPAQUE 180, 240, and 300 administered orally and rectally is supported by controlled studies in adults for examination of the GI tract, in addition to clinical studies in pediatric patients undergoing examination of the GI tract.

Oral Use in Conjunction with Intravenous Use

Diluted OMNIPAQUE Injection
The safety and effectiveness of OMNIPAQUE injection diluted to concentrations from 9 to 21 mg iodine/mL administered orally in conjunction with OMNIPAQUE injection administered intravenously for CT of the abdomen have been established in pediatric patients from birth to 17 years of age. Use is supported by clinical trials in adults, in addition to clinical studies in 69 pediatric patients undergoing CT of the abdomen after oral administration of diluted OMNIPAQUE plus intravenous administration of OMNIPAQUE.

OMNIPAQUE Oral Solution
The safety and effectiveness of OMNIPAQUE oral solution 9 and 12 administered orally in conjunction with OMNIPAQUE injection administered intravenously for CT of the abdomen in pediatric patients have been established in pediatric patients from birth to 17 years of age. Use is supported by the data establishing safety and effectiveness for OMNIPAQUE injection diluted and administered orally in conjunction with OMNIPAQUE injection administered intravenously for CT of the abdomen in pediatric patients.

Intraarticular Use
The safety and effectiveness of OMNIPAQUE have not been established in pediatric patients for arthrography.

Body Cavity Use
OMNIPAQUE 240, 300, 350 diluted to concentrations from 50 mg iodine/mL to 100 mg iodine/mL is indicated for use in pediatric patients from birth to 17 years of age for voiding cystourethrography (VCU). The use for voiding cystourethrography is supported by clinical studies in 51 pediatric patients undergoing VCU. The safety and effectiveness of OMNIPAQUE have not been established in pediatric patients for ERCP, herniography, or hysterosalpingography.

In general, the frequency of adverse reactions in pediatric patients was similar to that seen in adults *[see Adverse Reactions (6.1)]*. Pediatric patients at higher risk of experiencing adverse events during contrast-medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Thyroid function tests indicative of thyroid dysfunction, characterized by hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration in pediatric patients, including term and preterm neonates. Some patients were treated for hypothyroidism. Monitor pediatric patients 0 to 3 years of age closely, particularly those with one or more potential risk factors, for thyroid dysfunction *[see Warnings and Precautions (5.9) and Adverse Reactions (6.2)]*.

8.5 Geriatric Use

In clinical studies of OMNIPAQUE for CT, 52/299 (17%) of patients were 70 and over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

10.1 Intravascular Administration

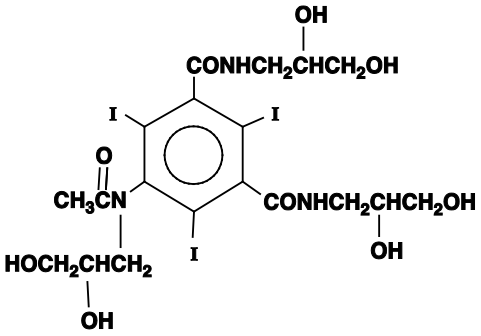
The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms included: cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy. Iohexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin and can be dialyzed.

11 DESCRIPTION

11.1 Chemical Characteristics

OMNIPAQUE (iohexol) injection is a nonionic, x-ray or radiographic contrast medium for intrathecal, intravenous, oral, rectal and body cavity use. OMNIPAQUE oral solution is for oral use only.

OMNIPAQUE injection and OMNIPAQUE oral solution are both provided as sterile, pyrogen-free and gluten-free solutions. OMNIPAQUE injection and OMNIPAQUE oral solution are colorless to pale yellow solutions. The chemical name of iohexol is Bis(2,3-dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)-acetamido]-2,4,6- triiodoisophthalamide with a molecular weight of 821.14 (iodine content 46.36%). Iohexol has the following structural formula:



OMNIPAQUE injection is available in five strengths:

- OMNIPAQUE 140 mg iodine/mL (302 mg of iohexol/mL): Each mL contains 140 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 180 mg iodine/mL (388 mg of iohexol/mL): Each mL contains 180 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 240 mg iodine/mL (518 mg of iohexol/mL): Each mL contains 240 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 300 mg iodine/mL (647 mg of iohexol/mL): Each mL contains 300 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE 350 mg iodine/mL (755 mg of iohexol/mL): Each mL contains 350 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium

OMNIPAQUE oral solution is available in two strengths:

- OMNIPAQUE oral solution 9 mg iodine/mL (19 mg of iohexol/mL): Each mL contains 9 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium
- OMNIPAQUE oral solution 12 mg iodine/mL (26 mg of iohexol/mL): Each mL contains 12 mg organically bound iodine, 1.21 mg tromethamine and 0.1 mg edetate calcium disodium

The pH is adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. OMNIPAQUE injection and OMNIPAQUE oral solution are sterilized by autoclaving and contain no preservatives.

11.2 Physical Characteristics

OMNIPAQUE injection and OMNIPAQUE oral solution have the following physical properties:

Presentation	Concentration (mg iodine/mL)	Osmolality* (mOsmol/kg water)	Absolute Viscosity (cP)		Specific Gravity
			20°C	37°C	37°C
OMNIPAQUE 140	140	322	2.3	1.5	1.164
OMNIPAQUE 180	180	408	3.1	2.0	1.209
OMNIPAQUE 240	240	520	5.8	3.4	1.280
OMNIPAQUE 300	300	672	11.8	6.3	1.349
OMNIPAQUE 350	350	844	20.4	10.4	1.406
OMNIPAQUE oral solution 9	9	38	1.1	0.8	1.011
OMNIPAQUE oral solution 12	12	45	1.1	0.8	1.014
**By vapor-pressure osmometry.*					

OMNIPAQUE 140, OMNIPAQUE 180, OMNIPAQUE 240, OMNIPAQUE 300, and OMNIPAQUE 350 have osmolalities from approximately 1.1 to 3.0 times that of plasma (285 mOsmol/kg water) or cerebrospinal fluid (301 mOsmol/kg water) as shown in the above table and are hypertonic under conditions of use.

OMNIPAQUE oral solution 9 and OMNIPAQUE oral solution 12 are hypotonic under conditions of use (see table above).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The iodine atoms in iohexol provide attenuation of X-rays in direct proportion to the concentration of iohexol. Since concentration changes over time, iohexol provides time-dependent image contrast which may assist in visualizing body structures.

12.2 Pharmacodynamics

Intrathecal Administration
The initial concentration and volume of the contrast medium, in conjunction with patient manipulation and the volume of cerebrospinal fluid (CSF) into which the contrast medium is placed, will determine the extent of the contrast that can be achieved. Following intrathecal injection in conventional radiography, OMNIPAQUE 180, 240, and 300 will continue to provide contrast for at least 30 minutes. Slow diffusion of iohexol takes place throughout the CSF with subsequent absorption into the bloodstream. At approximately 1 hour following injection, contrast will no longer be sufficient for conventional myelography.

After administration into the lumbar subarachnoid space, computerized tomography shows the presence of contrast medium in the thoracic region in about 1 hour, in the cervical region in about 2 hours, and in the basal cisterns in 3 to 4 hours.

Intravascular Administration
Following intravascular administration of OMNIPAQUE, the degree of contrast enhancement is directly related to the iodine concentration of an administered dose; peak iodine blood concentrations occur immediately (15 seconds to 120 seconds) following rapid intravenous injection. The time to maximum contrast enhancement can vary, depending on the organ, from the time that peak blood iodine concentrations are reached to one hour after intravenous bolus administration. When a delay between peak blood iodine concentrations and peak contrast is present, it suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine containing agent within the lesion and outside the blood pool.

Oral Administration
Orally administered OMNIPAQUE produces visualization of the gastrointestinal tract. Less than 1% of orally administered iohexol is recovered in the urine, suggesting minimal amounts are absorbed from the normal gastrointestinal tract. This amount may increase in the presence of bowel perforation or bowel obstruction.

Intraarticular Administration
Visualization of the joint spaces can be accomplished by direct injection of contrast medium. For intraarticular cavities, the injected iohexol is absorbed into the surrounding tissue and subsequently absorbed into systemic circulation.

Body Cavity Administration
For most body cavities, the injected iohexol is absorbed into the surrounding tissue and subsequently absorbed into systemic circulation. Examinations of the uterus (hysterosalpingography) and bladder (voiding cystourethrography) involve the almost immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure.

12.3 Pharmacokinetics

Following the intravenous administration of iohexol (between 500 mg iodine/kg to 1500 mg iodine/kg) to 16 adult human subjects, apparent first-order terminal elimination half-life was 12.6 hrs and total body clearance was 131 (98 to 165) mL/min. Clearance was not dose dependent.

Absorption

As evidenced by the amount recovered in urine, <1% of orally administered iohexol is absorbed from the normal gastrointestinal tract. This amount may increase in the presence of bowel perforation or bowel obstruction.

Distribution

In 16 adult subjects (receiving between 500 mg iodine/kg to 1500 mg iodine/kg intravenous iohexol) the plasma volume of distribution was165 (108 to 219) mL/kg.

In five adult patients receiving 16 mL to 18 mL of OMNIPAQUE (180 mg iodine/mL) by lumbar intrathecal injection the plasma volume of distribution was 559 (350 to 849) mL/kg.

Elimination

Metabolism
No significant metabolism, deiodination or biotransformation occurs.

Excretion
Following intravascular or intrathecal administration, iohexol is excreted unchanged by glomerular filtration. Approximately 90% of the intravenously injected iohexol dose is excreted within the first 24 hours. Following intravascular administration, peak urine concentration occurs in the first hour after injection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed with iohexol to evaluate carcinogenic potential. Iohexol was not genotoxic in a series of studies, including the Ames test, the mouse lymphoma TK locus forward mutation assay, and a mouse micronucleus assay. Iohexol did not impair the fertility of male or female rats when repeatedly administered at intravenous dosages up to 4 g iodine/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Volume/Concentration	Configuration	NDC
OMNIPAQUE 140 (140 mg iodine/mL) – Boxes of 10		
50 mL	+*PLUS*PAK™ (polymer bottle)	0407-1401-52
OMNIPAQUE 180 (180 mg iodine/mL) – Boxes of 10		
10 mL	Glass Vial	0407-1411-10
20 mL	Glass Vial	0407-1411-20
OMNIPAQUE 240 (240 mg iodine/mL) – Boxes of 10		
10 mL	Glass Vial	0407-1412-10
20 mL	Glass Vial	0407-1412-20
50 mL	+*PLUS*PAK™ (polymer bottle)	0407-1412-30

Volume/Concentration	Configuration	NDC
100 mL	+*PLUS*PAK™ (polymer bottle)	0407-1412-33
150 mL fill in 200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1412-34
200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1412-35
OMNIPAQUE 300 (300 mg iodine/mL) – Boxes of 10		
10 mL	Glass Vial	0407-1413-10
30 mL fill in 50 mL	+*PLUS*PAK™ (polymer bottle)	0407-1413-59
50 mL	+*PLUS*PAK™ (polymer bottle)	0407-1413-61
75 mL fill in 100 mL	+*PLUS*PAK™ (polymer bottle)	0407-1413-62
100 mL	+*PLUS*PAK™ (polymer bottle)	0407-1413-63
125 mL fill in 150 mL	Glass Bottle	0407-1413-53
125 mL fill in 200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1413-69
150 mL fill in 200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1413-65
200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1413-66
OMNIPAQUE 350 (350 mg iodine/mL) – Boxes of 10		
50 mL	+*PLUS*PAK™ (polymer bottle)	0407-1414-89
75 mL fill in 100 mL	+*PLUS*PAK™ (polymer bottle)	0407-1414-90
100 mL	+*PLUS*PAK™ (polymer bottle)	0407-1414-91
125 mL fill in 150 mL	Glass Bottle	0407-1414-76
125 mL fill in 200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1414-95
150 mL fill in 200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1414-93
200 mL	+*PLUS*PAK™ (polymer bottle)	0407-1414-94
OMNIPAQUE Oral Solution 9 (9 mg iodine/mL) – Boxes of 10		
500 mL	+*PLUS*PAK™ (polymer bottle)	0407-1415-09
OMNIPAQUE Oral Solution 12 (12 mg iodine/mL) – Boxes of 10		
500 mL	+*PLUS*PAK™ (polymer bottle)	0407-1416-12

The container closure system components (bottle, vial, stopper and cap) of OMNIPAQUE injection and OMNIPAQUE oral solution are not made with natural rubber latex.

16.2 Storage and Handling

Protect OMNIPAQUE glass vials and bottles and +*PLUS*PAK™ polymer bottles from light. Do not freeze. Discard any product that is inadvertently frozen, as freezing may compromise the closure integrity of the immediate container.

OMNIPAQUE Injection 140, 180, 240, 300 and 350

Store at controlled room temperature, 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. May be stored in a contrast media warmer for up to one month at 36° to 38°C (96.8° to 100.4°F).

OMNIPAQUE Oral Solution 9 and 12

Store between 0° and 30°C (32° to 86°F).

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions
Advise the patient concerning the risk of hypersensitivity reactions that can occur both during and after OMNIPAQUE administration. Advise the patient to report any signs or symptoms of hypersensitivity reactions during the procedure and to seek immediate medical attention for any signs or symptoms experienced after discharge *[see Warnings and Precautions (5.3)]*

Advise patients to inform their physician if they develop a rash after receiving OMNIPAQUE *[see Warnings and Precautions (5.12)]*.

Contrast-Induced Acute Kidney Injury
Advise the patient concerning appropriate hydration to decrease the risk of contrast-induced acute kidney injury *[see Warnings and Precautions (5.4)]*.

Extravasation
If extravasation occurs during injection, advise patients to seek medical care for progression of symptoms *[see Warnings and Precautions (5.7)]*.

Lactation
Advise a lactating woman that interruption of breastfeeding is not necessary. However, to avoid any exposure, a lactating woman may consider pumping and discarding breast milk for 10 hours after OMNIPAQUE administration *[see Use in Specific Populations (8.2)]*.

Thyroid Dysfunction
Advise parents/caregivers about the risk of developing thyroid dysfunction after OMNIPAQUE administration. Advise parents/caregivers about when to seek medical care for their child to monitor for thyroid function *[see Warnings and Precautions (5.9)]*.

GE Healthcare

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Product of Norwegian Origin.

GE Healthcare

OMNIPAQUE™ (iohexol) Injection

300 | 350

PHARMACY BULK PACKAGE–NOT FOR DIRECT INFUSION

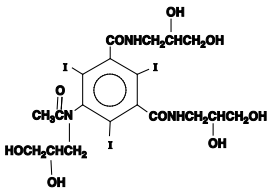
Section I —Intrathecal
Section II —Intravascular
Section III —Oral/Body Cavity Use

350	NOT FOR INTRATHECAL USE

R_x ONLY

DESCRIPTION

Iohexol, *N,N´* - Bis(2,3-dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodoisophthalamide, is a nonionic, water-soluble radiographic contrast medium with a molecular weight of 821.14 (iodine content 46.36%). In aqueous solution each triiodinated molecule remains undissociated. The chemical structure is:



OMNIPAQUE is provided as a sterile, pyrogen-free, colorless to pale-yellow solution, in Pharmacy Bulk Package, in the following iodine concentrations: 300 and 350 mg Iodine/mL. A Pharmacy Bulk Package is used to dispense multiple single doses, utilizing a suitable transfer device. OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL; and OMNIPAQUE 350 contains 755 mg of iohexol equivalent to 350 mg of organic iodine per mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. All solutions are sterilized by autoclaving and contain no preservatives. Iohexol solution is sensitive to light and therefore should be protected from exposure.

The available concentrations have the following physical properties:

Concentration (mg Iodine/mL)	Osmolality* (mOsm/kg water)	Osmolarity (mOsm/L)	Absolute Viscosity (cp)		Specific Gravity
			20°C	37°C	37°C
300	672	465	11.8	6.3	1.349
350	844	541	20.4	10.4	1.406

* By vapor-pressure osmometry.

OMNIPAQUE 300 and OMNIPAQUE 350 have osmolalities from approximately 2.2 to 3 times that of plasma (285 mOsm/kg water) or cerebrospinal fluid (301 mOsm/kg water) as shown in the above table and are hypertonic under conditions of use.

SECTION I
CLINICAL PHARMACOLOGY—Intrathecal

Iohexol is absorbed from cerebrospinal fluid (CSF) into the bloodstream and is eliminated by renal excretion. No significant metabolism, deiodination, or biotransformation occurs.

The initial concentration and volume of the medium, in conjunction with appropriate patient manipulation and the volume of CSF into which the medium is placed, will determine the extent of the diagnostic contrast that can be achieved.

Following intrathecal injection in conventional radiography, OMNIPAQUE 300 will continue to provide good diagnostic contrast for at least 30 minutes. Slow diffusion of iohexol takes place throughout the CSF with subsequent absorption into the bloodstream. Once in the systemic circulation, iohexol displays little tendency to bind to serum or plasma proteins. At approximately 1 hour following injection, contrast of diagnostic quality will no longer be available for conventional myelography. If computerized tomographic (CT) myelography is to follow, consideration should be given to a delay of several hours to allow the degree of contrast to decrease.

After administration into the lumbar subarachnoid space, computerized tomography shows the presence of contrast medium in the thoracic region in about 1 hour, in the cervical region in about 2 hours, and in the basal cisterns in 3 to 4 hours.

In patients with renal impairment, depending on the degree of impairment, prolonged plasma iohexol levels may be anticipated due to decreased renal elimination.

INDICATIONS AND USAGE—Intrathecal

OMNIPAQUE 300 is indicated for intrathecal administration in adults including myelography (lumbar, thoracic, cervical, total columnar) and in contrast enhancement for computerized tomography (myelography, cisternography, ventriculography).

CONTRAINDICATIONS—Intrathecal

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol. Myelography should not be performed in the presence of significant local or systemic infection where bacteremia is likely. Intrathecal administration of corticosteroids with OMNIPAQUE is contraindicated. Because of the possibility of overdosage, immediate repeat myelography in the event of technical failure is contraindicated (see DOSAGE AND ADMINISTRATION).

WARNINGS—General

SEVERE ADVERSE EVENTS - INADVERTENT INTRATHECAL ADMINISTRATION

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to ensure that OMNIPAQUE 350 is not administered intrathecally. (OMNIPAQUE 300 is approved for intrathecal administration).

If grossly bloody CSF is encountered, the possible benefits of a myelographic procedure should be considered in terms of the risk to the patient.

Caution is advised in patients with a history of epilepsy, severe cardiovascular disease, chronic alcoholism, or multiple sclerosis.

Elderly patients may present a greater risk following myelography. The need for the procedure in these patients should be evaluated carefully. Special attention must be paid to dose and concentration of the medium, hydration, and technique used.

Patients who are receiving anticonvulsants should be maintained on this therapy. Should a seizure occur, intravenous diazepam or phenobarbital sodium is recommended. In patients with a history of seizure activity who are not on anticonvulsant therapy, premedication with barbiturates should be considered.

Prophylactic anticonvulsant treatment with barbiturates should be considered in patients with evidence of inadvertent intracranial entry of a large or concentrated bolus of the contrast medium since there may be an increased risk of seizure in such cases.

Drugs which lower the seizure threshold, especially phenothiazine derivatives, including those used for their antihistamine properties, are not recommended for use with OMNIPAQUE. Drugs which lower the seizure thresh old, especially phenothiazine derivatives, including those used for their antihistamine properties, are not recommended for use with OMNIPAQUE. Others include MAO inhibitors, tricyclic antidepressants, CNS stimulants, and psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. While the contributory role of these medications has not been established, the use of such drugs should be based on physician evaluation of potential benefits and potential risks. Physicians have discontinued these agents at least 48 hours before and for at least 24 hours postprocedure.

Care is required in patient management to prevent inadvertent intracranial entry of a large dose or concentrated bolus of the medium. Also, effort should be directed to avoid rapid dispersion of the medium causing inadvertent rise to intracranial levels (eg, by active patient movement). Direct intracisternal or ventricular administration for standard radiography (not CT) is not recommended.

In most reported cases of major motor seizures with nonionic myelographic media, one or more of the following factors were present. Therefore avoid:

- Deviations from recommended procedure or in myelographic management.
- Use in patients with a history of epilepsy.
- Overdosage.
- Intracranial entry of a bolus or premature diffusion of a high concentration of the medium.
- Medication with neuroleptic drugs or phenothiazine antinauseants.
- Failure to maintain elevation of the head during the procedure, on the stretcher, or in bed.
- Excessive and particularly active patient movement or straining.

PRECAUTIONS—General

Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions have occurred. (See ADVERSE REACTIONS.)

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 preexisting renal disease). Dehydration in these patients seems to be enhanced by the osmotic diuretic action of contrast agents. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid, cardiovascular or central nervous system reactions, should always be considered (see ADVERSE REACTIONS). Therefore, it is of utmost importance that a course of action be carefully planned in advance for the immediate treatment of serious reactions, and that adequate and appropriate facilities and personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS). Premedication with antihistamines or corticosteroids these patients should be considered. Pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

In patients with severe renal insufficiency or failure, compensatory biliary excretion of the drug is anticipated to occur, with a slow clearance into the bile. Patients with hepatorenal insufficiency should not be examined unless the possibility of benefit clearly outweighs the additional risk.

Administration of contrast media should be performed by qualified personnel familiar with the procedure and appropriate patient management (see PATIENT MANAGEMENT). Sterile technique must be used with any spinal puncture.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body (see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY).

Information for Patients (or if applicable, parents of pediatric patients)

Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant (see CLINICAL PHARMACOLOGY).
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease or known thyroid disorder (see WARNINGS).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including non-prescription drugs, before you are administered this drug.

Drug Interactions

Drugs which lower seizure threshold, especially phenothiazine derivatives including those used for their antihistaminic or antinauseant properties, are not recommended for use with OMNIPAQUE. Others include monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, CNS stimulants, psychoactive drugs described as analeptics, major tranquilizers, or antipsychotic drugs. Such medications should be discontinued at least 48 hours before myelography, should not be used for the control of nausea or vomiting during or after myelography, and should not be resumed for at least 24 hours postprocedure. In nonelective procedures in patients on these drugs, consider prophylactic use of anticonvulsants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed with OMNIPAQUE to evaluate carcinogenic potential. OMNIPAQUE was not genotoxic in a series of studies, including the Ames test, the mouse lymphoma TK locus forward mutation assay, and a mouse micronucleus assay. OMNIPAQUE did not impair the fertility of male or female rats when administered at dosages up to 4 g Iodine/kg (2.3 times the maximum recommended dose for a 50 kg human, or approximately 0.4 times the maximum recommended dose for a 50 kg human following normalization of the data to body surface area estimates.)

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies performed in rats and rabbits at dosages up to 4 g Iodine/kg and 2.5 g Iodine/kg, respectively [2.3 and 1.4 times the maximum recommended dose for a 50 kg human, or approximately 0.4 (rat) and 0.5 (rabbit) times the maximum recommended dose for a 50 kg human following normalization of the data to body surface area estimates] have not revealed evidence of impaired fertility or harm to the fetus due to OMNIPAQUE. Adequate and well-controlled studies in pregnant women have not been conducted. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS—Intrathecal

The most frequently reported adverse reactions with OMNIPAQUE are headache, backache, neckache and stiffness, nausea, and vomiting. These reactions usually occur 1 to 10 hours after injection, and almost all occur within 24 hours. They usually last for a few hours, and usually disappear within 24 hours. Severe headaches persisting for days have been reported. Headache is often accompanied by nausea and vomiting and tends to be more frequent and persistent in patients not optimally hydrated.

Transient alterations in vital signs may occur and their significance must be assessed on an individual basis. Those reactions reported in clinical studies with OMNIPAQUE are listed below in decreasing order of occurrence, based on clinical studies of 1531 patients.

Headaches: The most frequently occurring adverse reaction following myelography has been headache, with an incidence of approximately 18%. Headache may be caused by either a direct effect of the contrast medium or by CSF leakage at the dural puncture site. However, in managing the patient, it is considered more important to minimize intracranial entry of contrast medium by postural management than attempting to control possible CSF leakage (see PATIENT MANAGEMENT).

Pain: Backache, neckache and stiffness, and neuralgia occurred following injection with an incidence of about 8%.

Nausea and Vomiting: Nausea was reported with an incidence of about 6%, and vomiting about 3% (see PATIENT MANAGEMENT). Maintaining normal hydration is very important.The use of phenothiazine antinauseants is not recommended. (See WARNINGS—General.) Reassurance to the patient that the nausea will clear usually is all that is required.

Dizziness: Transient dizziness was reported in about 2% of the patients.

Other Reactions: Other reactions occurring with an individual incidence of less than 0.1% included: feeling of heaviness, hypotension, hypertonia, sensation of heat, sweating, vertigo, loss of appetite, drowsiness, hypertension, photophobia, tinnitus, neuralgia, paresthesia, difficulty in micturition, and neurological changes.

General Adverse Reactions to Contrast Media

Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above, particularly the following reactions which have been reported in the literature for nonionic, water-soluble myelographic media including iohexol. These have included, but are not limited to, convulsion, aseptic and bacterial meningitis, and CNS and other neurological disturbances.

An aseptic meningitis syndrome has been reported (in less than 0.01%). It was usually preceded by pronounced headaches, nausea and vomiting. Onset usually occurred about 12 to 18 hours postprocedure. Prominent features were meningismus, fever, sometimes with oculomotor signs and mental confusion. Lumbar puncture revealed a high white cell count, high protein content often with a low glucose level and with absence of organisms. The condition usually started to clear spontaneously about 10 hours after onset, with complete recovery over 2 to 3 days.

Allergy or Idiosyncrasy: Chills, fever, profuse diaphoresis, pruritus, urticaria, nasal congestion, dyspnea, anaphylactic reactions, anaphylactic shock, and a case of Guillain-Barré syndrome.

CNS Irritation: Transient perceptual aberrations such as hallucinations, depersonalization, amnesia, hostility, amblyopia, diplopia, photophobia, psychosis, insomnia, anxiety, depression, hyperesthesia, visual or auditory or speech disturbances, confusion and disorientation. In addition, malaise, weakness, convulsion, EEG changes, meningism, hyperreflexia or areflexia, hypertonia or flaccidity, hemiplegia, paralysis, quadriplegia, restlessness, tremor, echoacousia, echolalia, asterixis, cerebral hemorrhage, and dysphasia have occurred.

Profound mental disturbances have also been reported. They consisted of various forms and degrees of aphasia, mental confusion, or disorientation. The onset is usually at 8 to 10 hours and lasts for about 24 hours, without aftereffects. Apprehension, agitation, or progressive withdrawal in several instances to the point of somnolence, stupor, and coma have been reported, as well as transitory hearing loss or other auditory symptoms and visual disturbances, including unilateral or bilateral loss of vision which may last for hours. In one case, persistent cortical loss of vision has been reported in association with convulsions. Ventricular block has been reported; amnesia of varying degrees may be present for the reaction event.

Persistent though transitory weakness in the leg or ocular muscles has been reported.

Peripheral neuropathies have been reported. They include sensory and/or motor or nerve root disturbances, myelitis, persistent leg muscle pain or weakness, 6th nerve palsy, or cauda equina syndrome. Muscle cramps, fasciculation or myoclonia, spinal convulsion, or spasticity responded promptly to a small intravenous dose of diazepam.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Severe, life-threatening, fatal anaphylactic shock has been reported.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations. Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

OVERDOSAGE

Clinical consequences of overdosage with OMNIPAQUE have not been reported. However, based on experience with other nonionic myelographic media, physicians should be alert to a potential increase in frequency and severity of CNS-mediated reactions. Even use of a recommended dose can produce effects tantamount to overdosage, if incorrect management of the patient during or immediately following the procedure permits inadvertent early intracranial entry of a large portion of the medium.

The intracisternal LD_{50} value of OMNIPAQUE (in grams of iodine per kilogram body weight) is greater than 2 in mice.

DOSAGE AND ADMINISTRATION —Intrathecal

The volume and concentration of OMNIPAQUE 300 to be administered will depend on the degree and extent of contrast required in the area(s) under examination and on the equipment and technique employed.

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is recommended for the examination of the lumbar, thoracic, and cervical regions in adults by lumbar or direct cervical injection and is slightly hypertonic to CSF.

A total dose of 3060 mg iodine or a concentration of 300 mg Iodine/mL should not be exceeded in adults in a single myelographic examination. This is based on clinical trial evaluation to date. As in all diagnostic procedures, the minimum volume and dose to produce adequate visualization should be used. Most procedures do not require either maximum dose or concentration.

Anesthesia is not necessary. Premedication sedatives or tranquilizers are usually not needed (see PRECAUTIONS). Patients should be well hydrated prior to and following contrast administration. Seizure-prone patients should be maintained on anticonvulsant medication. Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, concurrent drugs should not be physically admixed with contrast agents.

Rate of Injection: To avoid excessive mixing with CSF and consequent dilution of contrast, injection should be made slowly over 1 to 2 minutes.

Depending on the estimated volume of contrast medium which may be required for the procedure a small amount of CSF may be removed to minimize distention of the subarachnoid spaces.

The lumbar or cervical puncture needle may be removed immediately following injection since it is not necessary to remove OMNIPAQUE after injection into the subarachnoid space. *Adults:* The usual recommended total doses for use in lumbar, thoracic, cervical, and total columnar myelography in adults are 1.2 g Iodine to 3 g Iodine as follows:

Procedure	Formulations	Concentration (mg Iodine/mL)	Volume (mL)	Dose (g Iodine)
Thoracic Myelography (via lumbar injection)	OMNIPAQUE 300	300	6-10	1.8-3.0
Cervical Myelography (via lumbar injection)	OMNIPAQUE 300	300	6-10	1.8-3.0
Cervical Myelography (via C1-2 injection)	OMNIPAQUE 300	300	4-10	1.2-3.0
Total Columnar Myelography (via lumbar injection)	OMNIPAQUE 300	300	6-10	1.8-3.0

Refer to DIRECTIONS FOR PROPER USE OF OMNIPAQUE PHARMACY BULK PACKAGE section for instructions.

Parenteral products should be inspected visually for particulate matter or discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Repeat Procedures: **If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body. An interval of at least 48 hours should be allowed before repeat examination; however, whenever possible, 5 to 7 days is recommended.**

PATIENT MANAGEMENT—Intrathecal

Suggestions for Usual Patient Management

Good patient management should be exercised at all times to minimize the potential for procedurally related complications.

Preprocedure

- Discontinuance of neuroleptic drugs (including phenothiazines, eg, chlorpromazine, prochlorperazine, and promethazine) at least 48 hours beforehand should be considered.
- Maintain normal diet up to 2 hours before procedure.
- Ensure hydration—fluids up to procedure.

During Procedure

- Use minimum dose and concentration required for satisfactory contrast (see DOSAGE AND ADMINISTRATION).
- In all positioning techniques keep the patient's head elevated above highest level of spine.
- Do not lower head of table more than 15° in moving contrast medium cranially.
- In patients with excessive lordosis, consider lateral position for injection and movement of the medium cephalad.
- Inject slowly (over 1 to 2 minutes) to avoid excessive mixing.
- To maintain as a bolus, move medium to distal area very slowly. Use fluoroscopic monitoring.
- Avoid intracranial entry of a bolus.
- Avoid early and high cephalad dispersion of the medium.
- Avoid abrupt or active patient movement to minimize excessive mixing of medium with CSF. Instruct patient to remain passive. Move patient slowly and only as necessary.

Postprocedure

- Raise head of stretcher to at least 30° before moving patient onto it.
- Movement onto and off the stretcher should be done slowly with the patient completely passive, maintaining head-up position.
- Before moving patient onto bed, raise head of bed 30° to 45°.
- Advise patient to remain still in bed, in a sitting or semisitting position, especially in the first few hours.
- Maintain close observation for at least 12 hours after myelogram.
- Obtain visitors' cooperation in keeping the patient quiet and in head-up position, especially in first few hours.
- Encourage oral fluids. Diet as tolerated.
- If nausea or vomiting occurs, do not use phenothiazine antinauseants. Persistent nausea and vomiting will result in dehydration. Therefore, prompt consideration of replacement by intravenous fluids is recommended.

Alternative Postprocedure Method

- Recent evidence with nonionic, water-soluble contrast media suggests that maintaining the patient postmyelography in an upright position (via wheelchair or ambulation) may help minimize adverse effects. The upright position may help to delay upward dispersion of the medium and to maximize the spinal arachnoid absorption.

SECTION II

CLINICAL PHARMACOLOGY—Intravascular

Following intravascular injection, iohexol is distributed in the extracellular fluid compartment and is excreted unchanged by glomerular filtration. It will opacify those vessels in the path of flow of the contrast medium permitting radiographic visualization of the internal structures until significant hemodilution occurs.

Approximately 90% or more of the injected dose is excreted within the first 24 hours, with the peak urine concentrations occurring in the first hour after administration. Plasma and urine iohexol levels indicate that the iohexol body clearance is due primarily to renal clearance. An increase in the dose from 500 mg Iodine/kg to 1500 mg Iodine/kg does not significantly alter the clearance of the drug. The following pharmacokinetic values were observed following the intravenous administration of iohexol (between 500 mg Iodine/kg to 1500 mg Iodine/kg) to 16 adult human subjects: renal clearance—120 (86-162) mL/min; total body clearance—131 (98-165) mL/min; and volume of distribution—165 (108-219) mL/kg.

Renal accumulation is sufficiently rapid that the period of maximal opacification of the renal passages may begin as early as 1 minute after intravenous injection. Urograms become apparent in about 1 to 3 minutes with optimal contrast occurring between 5 to 15 minutes.

In nephropathic conditions, particularly when excretory capacity has been altered, the rate of excretion may vary unpredictably, and opacification may be delayed after injection. Severe renal impairment may result in a lack of diagnostic opacification of the collecting system and, depending on the degree of renal impairment, prolonged plasma iohexol levels may be anticipated. In these patients, as well as in infants with immature kidneys, the route of excretion through the gallbladder and into the small intestine may increase.

Iohexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin. No significant metabolism, deiodination or biotransformation occurs.

OMNIPAQUE probably crosses the placental barrier in humans by simple diffusion. It is not known to what extent iohexol is excreted in human milk.

Animal studies indicate that iohexol does not cross an intact blood-brain barrier to any significant extent following intravascular administration.

OMNIPAQUE enhances computed tomographic imaging through augmentation of

radiographic efficiency. The degree of density enhancement is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid intravenous injection. Blood levels fall rapidly within 5 to 10 minutes and the vascular compartment half-life is approximately 20 minutes. This can be accounted for by the dilution in the vascular and extravascular fluid compartments which causes an initial sharp fall in plasma concentration. Equilibration with the extracellular compartments is reached in about ten minutes; thereafter, the fall becomes exponential.

The pharmacokinetics of iohexol in both normal and abnormal tissue have been shown to be variable. Contrast enhancement appears to be greatest immediately after bolus administration (15 seconds to 120 seconds). Thus, greatest enhancement may be detected by a series of consecutive two-to-three second scans performed within 30 to 90 seconds after injection (ie, dynamic computed tomographic imaging). Utilization of a continuous scanning technique (ie, dynamic CT scanning) may improve enhancement and diagnostic assessment of tumor and other lesions such as abscess, occasionally revealing unsuspected or more extensive disease. For example, a cyst may be distinguished from a vascularized solid lesion when precontrast and enhanced scans are compared; the nonperfused mass shows unchanged x-ray absorption (CT number). A vascularized lesion is characterized by an increase in CT number in the few minutes after a bolus of intravascular contrast agent; it may be malignant, benign, or normal tissue, but would probably not be a cyst, hematoma, or other nonvascular lesion.

Because unenhanced scanning may provide adequate diagnostic information in the individual patient, the decision to employ contrast enhancement, which may be associated with risk and increased radiation exposure, should be based upon a careful evaluation of clinical, other radiological, and unenhanced CT findings.

INDICATIONS AND USAGE

GENERAL—Intravascular

OMNIPAQUE 350 is indicated in adults for angiocardiography (ventriculography, selective coronary arteriography), aortography including studies of the aortic root, aortic arch, ascending aorta, abdominal aorta and its branches, intravenous digital subtraction angiography of the head, neck, abdominal, renal and peripheral vessels, peripheral arteriography, and excretory urography.

OMNIPAQUE 350 is indicated in pediatric patients for angiocardiography (ventriculography, pulmonary arteriography, and venography; studies of the collateral arteries and aortography, including the aortic root, aortic arch, ascending and descending aorta). OMNIPAQUE 300 is indicated in adults for aortography including studies of the aortic arch, abdominal aorta and its branches, cerebral arteriography, peripheral venography (phlebography), and excretory urography.

OMNIPAQUE 300 is indicated in pediatric patients for angiocardiography (ventriculography), excretory urography.

CONTRAINDICATIONS

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General

Nonionic iodinated contrast media inhibit blood coagulation, *in vitro,* less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

OMNIPAQUE should be used with extreme care in patients with severe functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Although neither the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available. Reports of thyroid storm following the use of iodinated contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

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

Younger age, very low birth weight, prematurity, and the presence of other conditions, such as, admission to neonatal or pediatric intensive care units, and cardiac conditions are associated with an increased risk. Pediatric patients with cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures, such as catheterization and computed tomography (CT).

Pediatric patients 0 to 3 years of age warrant closer monitoring because an underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. Evaluate thyroid function in all pediatric patients 0 to 3 years of age within 3 weeks following exposure to iodinated contrast media, especially in term and preterm neonates. If thyroid dysfunction is detected, treat and monitor thyroid function as clinically needed.

Severe Cutaneous Adverse Reactions: Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks after intravascular OMNIPAQUE administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agent; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering OMNIPAQUE to patients with a history of a severe cutaneous adverse reaction to OMNIPAQUE.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS—General

Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular—General).

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 preexisting renal disease), infants and small pediatric patients. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with preexisting renal disease) following excretory urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions should always be considered (see ADVERSE REACTIONS: Intravascular—General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular—General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids in these patients should be considered. Recent reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate or iothalamate- based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in

selected adult 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 which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended. Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients

Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant (see CLINICAL PHARMACOLOGY—Intravascular).
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including non-prescription drugs, before you are administered this drug.
5. Advise patients to inform their physician if they develop a rash after receiving OMNIPAQUE.
6. Advise parents/caregivers about the risk of developing thyroid dysfunction after OMNIPAQUE administration. Advise parents/caregivers about when to seek medical care for their child to monitor for thyroid function. [see WARNINGS]

Drug/Laboratory Test Interaction

If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected.

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed with OMNIPAQUE to evaluate carcinogenic potential. OMNIPAQUE was not genotoxic in a series of studies, including the Ames test, the mouse lymphoma TK locus forward mutation assay, and a mouse micronucleus assay. OMNIPAQUE did not impair the fertility of male or female rats when administered at dosages up to 4 g Iodine/kg (2.3 times the maximum recommended dose for a 50 kg human, or approximately 0.4 times the maximum recommended dose for a 50 kg human following normalization of the data to body surface area estimates.)

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies performed in rats and rabbits at dosages up to 4 g Iodine/kg and 2.5 g Iodine/kg, respectively [2.3 and 1.4 times the maximum recommended dose for a 50 kg human, or approximately 0.4 (rat) and 0.5 (rabbit) times the maximum recommended dose for a 50 kg human following normalization of the data to body surface area estimates] have not revealed evidence of impaired fertility or harm to the fetus due to OMNIPAQUE. Adequate and well-controlled studies in pregnant women have not been conducted. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age. Thyroid function tests indicative of thyroid dysfunction, characterized by hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration in pediatric patients, including term and preterm neonates. Some patients were treated for hypothyroidism. Monitor pediatric patients 0 to 3 years of age closely, particularly those with one or more potential risk factors, for thyroid dysfunction (see WARNINGS and ADVERSE REACTIONS).

ADVERSE REACTIONS: Intravascular—General

Serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media. *Cardiovascular System:* Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less.

Nervous System: Vertigo (including dizziness and lightheadedness) (0.5%), pain (3%), vision abnormalities (including blurred vision and photomas) (2%), headache (2%), and taste perversion (1%). Others including anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported, with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%). Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication.

Pediatrics

In controlled clinical trials involving 391 patients for pediatric angiocardiography and urography, adverse reactions following the use of OMNIPAQUE 300 and OMNIPAQUE 350 were generally not more frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).

Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion (0.3%).

Respiratory System: Congestion (0.3%) and apnea (0.3%).

Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).

Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media

Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above.

The following reactions have been reported after administration of - intravascular iodinated contrast media. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* transient proteinuria, oliguria or anuria. *Endocrine reactions:* hyperthyroidism, hypothyroidism. *Skin and Subcutaneous Tissue Disorders:* Reactions range from mild (e.g. rash, erythema, pruritus, urticaria, skin discoloration) to severe: [e.g. Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)]. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing and lacrimation, anaphylactic reactions and anaphylactic shock. Fatalities have occurred, due to this or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; *or to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema, especially facial cramps, neutropenia, and dizziness. Immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears two days after exposure and subsides by the sixth day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Severe, life-threatening, fatal anaphylactoid shock has been reported. Reported incidences of death range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 (0.01 percent). Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy are twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Immediately following intravascular injection of contrast medium, a transient sensation of mild warmth is not unusual. Warmth is less frequent with OMNIPAQUE than with ionic media. (see ADVERSE REACTIONS: Intravascular—General)

OVERDOSAGE

Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms included: cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION —General

As with all radiopaque contrast agents, the lowest dose of OMNIPAQUE necessary to obtain adequate visualization should be used. A lower dose may reduce the possibility of an adverse reaction. Most procedures do not require use of either the maximum volume or the highest concentration of OMNIPAQUE. The combination of volume and concentration of OMNIPAQUE to be used should be carefully individualized accounting for factors such as age, body weight, size of the vessel and the rate of blood flow within the vessel. Other factors such as anticipated pathology, degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed should be considered.

Sterile technique must be used in all vascular injections involving contrast media.

Refer to DIRECTIONS FOR PROPER USE OF OMNIPAQUE PHARMACY BULK PACKAGE section for instructions.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

It may be desirable that solutions of radiopaque diagnostic agents be used at body temperature when injected.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions of OMNIPAQUE should be used only if clear and within the normal colorless to pale yellow range. If particulate matter or discoloration is present, do not use.

INDIVIDUAL INDICATIONS AND USAGE

ANGIOCARDIOGRAPHY

Pharmacology—Hemodynamic Changes

OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated in adults for angiocardiography (ventriculography, aortic root injections, and selective coronary arteriography). OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated in pediatric patients for angiocardiography (ventriculography, pulmonary arteriography, and venography, and studies of the collateral arteries).

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is indicated in pediatric patients pediatric patients for angiocardiography (ventriculography).

After both ventricular and coronary injection, decreases in systolic pressure were less pronounced and returned to baseline values earlier with OMNIPAQUE 350 than with diatrizoate meglumine and diatrizoate sodium injection.

OMNIPAQUE 350 produced less Q-T interval prolongation than seen with diatrizoate meglumine and diatrizoate sodium injection.

In pediatric patients, after injection of all sites, but particularly following ventricular and pulmonary artery injections, decreases in both systolic and diastolic intravascular pressure were significantly less pronounced with OMNIPAQUE 350 than with diatrizoate meglumine and diatrizoate sodium injection. In pediatric patients OMNIPAQUE 350 produced significantly less shortening of the R-R interval than seen with diatrizoate meglumine and diatrizoate sodium injection.

If repeat injections are made in rapid succession, all these changes are likely to be more pronounced. (See DOSAGE AND ADMINISTRATION.)

Precautions

During administration of large doses of OMNIPAQUE 350, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the preexisting condition. Hypotension should be corrected promptly since it may induce serious arrhythmias. Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of the hemodynamic changes which may occur after injection into the right heart outflow tract. (See PRECAUTIONS—General.)

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Adverse Reactions

Cardiovascular system reactions in angiocardiography included angina (8%), hypotension (2.5%), bradycardia (1%), and tachycardia (1%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The individual dose or volume is determined by the size of the structure to be visualized, the anticipated degree of hemodilution, and valvular competence. Weight is a minor consideration in adults, but must be considered in infants and young pediatric patients. The volume of each individual injection is a more important consideration than the total dosage used. When large individual volumes are administered, as in ventriculography and aortography, it has been suggested that several minutes be permitted to elapse between each injection to allow for subsidence of possible hemodynamic disturbances.

The recommended single injection volume of OMNIPAQUE 350 for angiocardiographic procedures in adults and the recommended single injection volumes of OMNIPAQUE 350 and OMNIPAQUE 300 for angiographic procedures in pediatric patients are as follows:

Ventriculography

Adults: The usual adult volume for a single injection is 40 mL with a range of 30 mL to 60 mL. This may be repeated as necessary. When combined with selective coronary arteriography, the total administered volume should not exceed 250 mL (87.5 g Iodine).

Pediatrics: The usual single injection dose of OMNIPAQUE 350 is 1.25 mL/kg of body weight with a range of 1 mL/kg to 1.5 mL/kg. For OMNIPAQUE 300 the usual single injection dose is 1.75 mL/kg with a range of 1.5 mL/kg to 2.0 mL/kg. When multiple injections are given, the total administered dose should not exceed 5 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350 or up to a total volume of 291 mL of OMNIPAQUE 300.

Selective Coronary Arteriography

The usual adult volume for right or left coronary arteriography is 5 mL (range 3 mL to 14 mL) per injection.

Aortic Root and Arch Study When Used Alone

The usual adult single injection volume is 50 mL, with a range of 20 mL to 75 mL.

Pulmonary Angiography

Pediatrics: The usual single injection dose is 1 mL/kg of OMNIPAQUE 350.

Combined Angiocardiographic Procedures

Multiple Procedures

Adults: The visualization of multiple vascular systems and target organs is possible during a single radiographic examination of the patient.

Large doses of OMNIPAQUE 350 were well tolerated in angiographic procedures requiring multiple injections.

The maximum total volume for multiple procedures should not exceed 250 mL of 350 mg Iodine/mL (87.5 g Iodine).

Pediatrics: Visualization of multiple vascular systems and target organs is possible during a single radiographic examination of the patient.

The maximum total dose for multiple injection procedures should not exceed 5 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350 or 6 mL/kg up to a total volume of 291 mL of OMNIPAQUE 300.

AORTOGRAPHY AND SELECTIVE VISCERAL ARTERIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL and OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL are indicated in adults for use in aortography and selective visceral arteriography including studies of the aortic arch, ascending aorta, and abdominal aorta and its branches (celiac, mesenteric, renal, hepatic and splenic arteries).

OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated in pediatric patients for use in aortography including studies of the aortic root, aortic arch, ascending and descending aorta.

Precautions

Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows. (See PRECAUTIONS—General.)

Adverse Reactions

See ADVERSE REACTIONS: Intravascular—General, and ADVERSE REACTIONS ANGIOCARDIOGRAPHY.

Dosage and Administration

Adults: The usual adult volume as a single injection is 50 mL to 80 mL for the aorta, 30 mL to 60 mL for major branches including celiac and mesenteric arteries, and 5 mL to 15 mL for renal arteries. Repeated injections may be performed if indicated, but the total volume should not exceed 291 mL of OMNIPAQUE 300 or 250 mL of OMNIPAQUE 350 (87.5 g Iodine). *Pediatrics:* The usual single injection dose is 1.0 mL/kg of OMNIPAQUE 350 and should not exceed 5.0 mL/kg up to a total volume of 250 mL of OMNIPAQUE 350.

CEREBRAL ARTERIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is indicated in adults for use in cerebral arteriography.

The degree of pain and flushing as the result of the use of OMNIPAQUE 300 in cerebral arteriography is less than that seen with comparable injections of many contrast media.

In cerebral arteriography, patients should be appropriately prepared consistent with existing or suspected disease states.

Precautions

Cerebral arteriography should be undertaken with extreme care with special caution in elderly patients, patients in poor clinical condition, advanced arteriosclerosis, severe arterial hypertension, recent cerebral embolism or thrombosis, and cardiac

decompensation.

Since the contrast medium is given by rapid injection, the patient should be monitored for possible untoward reactions. (See PRECAUTIONS—General.)

Adverse Reactions

Cerebral arteriography with water-soluble contrast media has been associated with temporary neurologic complications including seizures, drowsiness, transient paresis, and mild disturbances in vision such as photomas of 1-second or less duration.

Central nervous system reactions in cerebral arteriography included photomas (15%), headache (5.5%), and pain (4.5%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

OMNIPAQUE 300 is recommended for cerebral arteriography at the following volumes: common carotid artery (6 mL to 12 mL), internal carotid artery (8 mL to 10 mL), external carotid artery (6 mL to 9 mL), and vertebral artery (6 mL to 10 mL).

DIGITAL SUBTRACTION ANGIOGRAPHY

Intravenous Administration

OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated in adults for use in intravenous digital subtraction angiography (I.V.DSA) of the vessels of the head, neck, and abdominal, renal and peripheral vessels.

Arteriograms of diagnostic quality can be obtained following the intravenous administration of contrast media employing digital subtraction and computer imaging enhancement techniques. The intravenous route of administration using these techniques has the advantage of being less invasive than the corresponding selective catheter placement of medium. The dose is administered into a peripheral vein, the superior vena cava or right atrium, usually by mechanical injection although sometimes by rapid manual injection. The technique has been used to visualize the ventricles, aorta and most of its larger branches, including the carotids, cerebrals, vertebrals, renal, celiac, mesenterics, and the major peripheral vessels of the limbs. Radiographic visualization of these structures is possible until significant hemodilution occurs.

OMNIPAQUE 350 can be injected intravenously as a rapid bolus to provide arterial visualization using digital subtraction radiography. Preprocedural medications are not considered necessary. OMNIPAQUE 350 has provided diagnostic arterial radiographs in about 95% of patients. In some cases, poor arterial visualization has been attributed to patient movement. OMNIPAQUE 350 is very well tolerated in the vascular system. Patient discomfort (general sensation of heat and/or pain) following injection is less than with various other contrast media.

Precautions

Since the contrast medium is usually administered mechanically under high pressure, rupture of smaller peripheral veins can occur. It has been suggested that this can be avoided by using an intravenous catheter threaded proximally beyond larger tributaries or, in the case of the antecubital vein, into the superior vena cava. Sometimes the femoral vein is used. (See PRECAUTIONS—General.)

Adverse Reactions

Cardiovascular system reactions in digital arteriography included transient PVCs (16%) and PACs (6.5%). (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The usual injection volume of OMNIPAQUE 350 for the intravenous digital technique is 30 mL to 50 mL of a 350 mg Iodine/mL solution. This is administered as a bolus at 7.5 to 30 mL/second using a pressure injector. The volume and rate of injection will depend primarily on the type of equipment and technique used.

Frequently three or more injections may be required, up to a total volume not to exceed 250 mL (87.5 g Iodine).

PERIPHERAL ANGIOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL or OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated in adults for use in peripheral arteriography. OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is indicated in adults for use in peripheral venography.

Sedative medication may be employed prior to use. Anesthesia is not considered necessary. Patient discomfort during and immediately following injection is substantially less than that following injection of various other contrast media. Moderate to severe discomfort is very unusual.

Precautions

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all. (See PRECAUTIONS—General.)

Adverse Reactions

A transient sensation of mild warmth is usual, immediately following injection. This has not interfered with the procedure.

In phlebography the incidence of leg pain was 21%. This usually was mild and lasted a short time after injection. (See ADVERSE REACTIONS: Intravascular—General.)

Dosage and Administration

The volume required will depend on the size, flow rate, and disease state of the injected vessel and on the size and condition of the patient, as well as the imaging technique used. The dosage recommended for use in peripheral angiography is as follows:

Aortofemoral runoffs:	20 mL to 70 mL of OMNIPAQUE 350 (350 mg Iodine/mL) 30 mL to 90 mL of OMNIPAQUE 300 (300 mg Iodine/mL)
Selective arteriograms: (femoral/iliac)	10 mL to 30 mL of OMNIPAQUE 350 (350 mg Iodine/mL) 10 mL to 60 mL of OMNIPAQUE 300 (300 mg Iodine/mL)
Venography (per leg):	40 mL to 100 mL of OMNIPAQUE 300 (300 mg Iodine/mL)

EXCRETORY UROGRAPHY

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL or OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated for use in adults in excretory urography to provide diagnostic contrast of the urinary tract.

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is indicated in pediatric patients for excretory urography. (See Section III for information on voiding cystourethrography.)

For pharmacokinetics of excretion in adults, see CLINICAL PHARMACOLOGY—Intravascular.

Precautions

Preparatory dehydration is not recommended in the elderly, pediatric patients, diabetic or azotemic patients, or in patients with suspected myelomatosis.

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Since there is a possibility of temporary suppression of urine formation, it is recommended that a suitable interval elapse before excretory urography is repeated, especially in patients with unilateral or bilateral reduction in renal function. (See PRECAUTIONS—General.)

Adverse Reactions

See ADVERSE REACTIONS: Intravascular—General.

Dosage and Administration

Adults: OMNIPAQUE 300 and OMNIPAQUE 350 at dosages from 200 mg Iodine/kg body weight to 350 mg Iodine/kg body weight have produced diagnostic opacification of the excretory system in patients with normal renal function.

Pediatrics

Excretory Urography

OMNIPAQUE 300 at doses of 0.5 mL/kg to 3 mL/kg of body weight has produced diagnostic opacification of the excretory tract. The usual dose for pediatric patients is 1 mL/kg to 1.5 mL/kg. Dosage for pediatric patients should be administered in proportion to age and body weight. The total administered dose should not exceed 3 mL/kg.

SECTION III

CLINICAL PHARMACOLOGY—Oral/Body Cavity Use

For most body cavities, the injected iohexol is absorbed into the surrounding tissue and eliminated by the kidneys and bowel as previously described in SECTION II, CLINICAL PHARMACOLOGY—Intravascular. Examinations of the uterus (hysterosalpingography) and bladder (voiding cystourethrography) involve the almost immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure.

Orally administered iohexol is very poorly absorbed from the normal gastrointestinal tract. Only 0.1 to 0.5 percent of the oral dose was excreted by the kidneys. This amount may increase in the presence of bowel perforation or bowel obstruction. Iohexol is well tolerated and readily absorbed if leakage into the peritoneal cavity occurs.

Visualization of the joint spaces, uterus, fallopian tubes, peritoneal herniations, pancreatic and bile ducts, and bladder can be accomplished by direct injection of contrast medium into the region to be studied. The use of appropriate iodine concentrations assures diagnostic density.

Orally administered OMNIPAQUE produces good visualization of the gastrointestinal tract. OMNIPAQUE is particularly useful when barium sulfate is contraindicated as in patients with suspected bowel perforation or those where aspiration of contrast medium is a possibility.

INDICATIONS AND USAGE, GENERAL—Oral/Body Cavity Use

OMNIPAQUE 300 and OMNIPAQUE 350 have osmolalities from approximately 2.4 to 3 times that of plasma (285 mOsm/kg water) and are hypertonic under conditions of use.

Adults: OMNIPAQUE 350 is indicated in adults for arthrography and oral pass-thru examination of the gastrointestinal tract.

OMNIPAQUE 300 is indicated in adults for arthrography and hysterosalpingography.

OMNIPAQUE diluted to concentrations from 6 mg Iodine/mL to 9 mg Iodine/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL administered intravenously is indicated in adults for contrast enhanced computed tomography of the abdomen.

Pediatric Patients: OMNIPAQUE 300 is indicated in pediatric patients for examination of the gastrointestinal tract.

OMNIPAQUE diluted to concentrations from 50 mg Iodine/mL to 100 mg Iodine/mL is indicated in pediatric patients for voiding cystourethrography.

OMNIPAQUE diluted to concentrations from 9 mg Iodine/mL to 21 mg Iodine/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL administered intravenously are indicated in pediatric patients for use in contrast enhanced computed tomography of the abdomen.

CONTRAINDICATIONS

OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General

See SECTION II, WARNINGS—General.

PRECAUTIONS—General

See SECTION II, PRECAUTIONS—General.

Orally administered hypertonic contrast media draw fluid into the intestines which, if

severe enough, could result in hypovolemia. Likewise, in pediatric patients, the occurrence of diarrhea may result in hypovolemia. Plasma fluid loss may be sufficient to cause a shock- like state which, if untreated, could be dangerous. This is especially pertinent to the elderly, cachectic patients of any age as well as infants and small pediatric patients.

ADVERSE REACTIONS: Oral/Body Cavity Use—General

Body Cavities

In controlled clinical trials involving 285 adult patients for various body cavity examinations using OMNIPAQUE 300 and 350, the following adverse reactions were reported.

Cardiovascular System Incidence > 1%: None Incidence ≤1%: Hypertension
Nervous System
Incidence > 1%: Pain (26%)
Incidence ≤ 1%: Headache, somnolence, fever, muscle weakness, burning, unwell feeling, tremors, lightheadedness, syncope
Respiratory System
None
Gastrointestinal System
Incidence > 1%: None
Incidence ≤ 1%: Flatulence, diarrhea, nausea, vomiting, abdominal pressure
Skin and Appendages
Incidence > 1%: Swelling (22%), heat (7%)
Incidence ≤ 1%: Hematoma at injection site
The most frequent reactions, pain and swelling, were almost exclusively reported after arthrography and were generally related to the procedure rather than the contrast medium.
Gastrointestinal reactions were almost exclusively reported after oral pass-thru examinations.
For additional information on adverse reactions that may be expected with specific procedures, see INDIVIDUAL INDICATIONS AND USAGE. For information on general adverse reactions to contrast media, see SECTION II, ADVERSE REACTIONS: Intravascular—General.

No adverse reactions associated with the use of OMNIPAQUE for VCU procedures were reported in 51 pediatric patients studied.

Oral Use

See INDIVIDUAL INDICATIONS AND USAGE: Oral Use—Adverse Reactions.

OVERDOSAGE
See also SECTION II, OVERDOSAGE.

The recommended dose of OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL for adult oral pass-thru examination of the gastrointestinal tract is 50 mL to 100 mL. In a Phase I study, 150 mL of OMNIPAQUE 350 was administered orally to 11 healthy male subjects. The incidence of diarrhea was 91% (10 of 11) and abdominal cramping was 27% (3 of 11). Despite all of these events being mild and transient the occurrences were more than double that seen at the recommended doses. It is apparent from this finding that larger volumes of hypertonic contrast media, like OMNIPAQUE, increase the osmotic load in the bowel which may result in greater fluid shifts.

DOSAGE AND ADMINISTRATION—General
See SECTION II, DOSAGE AND ADMINISTRATION—General.
INDIVIDUAL INDICATIONS AND USAGE

Oral Use

Adults: OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated in adults for use in oral pass-thru examination of the gastrointestinal tract. OMNIPAQUE diluted to concentrations from 6 mg Iodine/mL to 9 mg Iodine/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL administered intravenously are indicated in adults for use in contrast enhanced computed tomography of the abdomen. Dilute oral plus intravenous OMNIPAQUE may be useful when unenhanced imaging does not provide sufficient delineation between normal loops of the bowel and adjacent organs or areas of suspected pathology. *Pediatric patients:* OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL administered orally or rectally is indicated in pediatric patients for use in examination of the gastrointestinal tract. OMNIPAQUE diluted to concentrations from 9 mg Iodine/mL to 21 mg Iodine/mL administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL administered intravenously are indicated in pediatric patients for use in contrast enhanced computed tomography of the abdomen.

Precautions

See PRECAUTIONS—General.

Adverse Reactions

Oral administration of OMNIPAQUE is most often associated with mild, transient diarrhea especially when high concentrations and large volumes are administered. Nausea, vomiting, and moderate diarrhea have also been reported following orally administered OMNIPAQUE, but much less frequently. For CT examinations using dilute oral plus intravenous contrast medium, adverse events are more likely to be associated with the intravenous injection than the hypotonic oral solution. It should be noted that serious or anaphylactoid reactions that may occur with intravascular iodinated media are possible following administration by other routes.

Adults: In controlled clinical trials involving 54 adult patients for oral pass-thru examination of the gastrointestinal tract using OMNIPAQUE 350, the following adverse reactions were reported: diarrhea (42%), nausea (15%), vomiting (11%), abdominal pain (7%), flatulence (2%), and headache (2%). In controlled clinical studies involving 44 adult patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (2%). Pediatric patients: In controlled clinical studies involving 58 pediatric patients for examination of the gastrointestinal tract at a concentration of 300 mg Iodine/mL, the following adverse reactions were reported: diarrhea (36%), vomiting (9%), nausea (5%), fever (5%), hypotension (2%), abdominal pain (2%), and urticaria (2%). In clinical studies an increased frequency and severity of diarrhea was noted with an increase in the administered concentration and dose of the radiocontrast agent. In controlled clinical studies involving 69 pediatric patients for dilute oral plus intravenous CT examination of the gastrointestinal tract using OMNIPAQUE 300, adverse reactions were limited to a single report of vomiting (1.4%).

Dosage and Administration

Adults: The recommended dosage of undiluted OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL for oral pass-thru examination of the gastrointestinal tract in adults is 50 mL to 100 mL depending on the nature of the examination and the size of the patient. The recommended oral dosage of OMNIPAQUE diluted to concentrations of 6 mg Iodine/mL to 9 mg Iodine/mL for contrast enhanced computed tomography of the abdomen in adults is 500 mL to 1000 mL. Smaller administered volumes are needed as the concentration of the final solution is increased (see Table below). In conjunction with dilute oral administration, the recommended dosage of OMNIPAQUE 300 intravenously is 100 mL to 150 mL. The oral dose is administered about 20 to 40 minutes prior to the intravenous dose and image acquisition.

Pediatric Patients: The dosage of undiluted OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL, is dependent on the nature of the examination and the size of the patient. Based on clinical experience, it is recommended that OMNIPAQUE 180 (available in single use vials), be used in pediatric patients less than 3 months of age. OMNIPAQUE 300 may be used in pediatric patients 3 months of age and older.

The following dosage guidelines are recommended:

Age	Volume of OMNIPAQUE
Less than 3 months	5 —30 mL
Three months to 3 years	Up to 60 mL
Four years to 10 years	Up to 80 mL
Greater than 10 years	Up to 100 mL

When given rectally, larger volumes may be used.

The recommended oral dosage of OMNIPAQUE diluted to concentrations of 9 mg Iodine/mL to 21 mg Iodine/mL for contrast computed tomography of the abdomen in pediatric patients is 180 mL to 750 mL. Smaller administered volumes are needed as the concentration of the final solution is increased (see Table below). The total oral dose in grams of iodine should generally not exceed 5 g Iodine for pediatric patients under 3 years of age and 10 g Iodine for pediatric patients from 3 to 18 years of age. The oral dosage may be given all at once or over a period of 30 to 45 minutes if there is difficulty in consuming the required volume. In conjunction with dilute oral administration the recommended dosage of OMNIPAQUE 300 is 2mL/kg when administered intravenously with a range of 1 mL/kg to 2 mL/kg. Dosage pediatric patients should be administered in proportion to age and body weight. The total intravenously administered dose should not exceed 3 mL/kg. The oral dose is administered about 30 to 60 minutes prior to the intravenous dose and image acquisition.

OMNIPAQUE may be diluted with water or beverage as follows:

To Achieve	Add		To
One Liter of Contrast Medium at A Final Concentration (mg Iodine/mL) of	Stock Concentration of OMNIPAQUE (mg Iodine/mL)	Volume (mL)	Water, Carbonated Beverage, Milk, or Juice (mL)
6	300	20	980
	350	17	983
9	300	30	970
	350	26	974
12	300	40	960
	350	35	965
15	300	50	950
	350	43	957
18	300	60	940
	350	52	948
21	300	70	930
	350	60	940

Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

VOIDING CYSTOURETHROGRAPHY (VCU)

OMNIPAQUE diluted to concentrations from 50 mg Iodine/mL to 100 mg Iodine/mL is indicated in pediatric patients for voiding cystourethrography. VCUs are often performed in conjunction with excretory urography.

Precautions

See PRECAUTIONS—General.

Since the VCU procedure requires instrumentation, special precautions should be observed in those patients known to have an acute urinary tract infection. Filling of the bladder should be done at a steady rate, exercising caution to avoid excessive pressure. Sterile procedures are essential.

Adverse Reactions

See ADVERSE REACTIONS—General.

Dosage and Administration

OMNIPAQUE may be diluted, utilizing aseptic technique, with Sterile Water for Injection to a concentration of 50 mg Iodine/mL to 100 mg Iodine/mL for voiding cystourethrography. The concentration may vary depending upon the patient's size and age and also with the technique and equipment used. Sufficient volume of contrast medium should be administered to adequately fill the bladder. The usual volume ranges from 50 mL to 300 mL of OMNIPAQUE at a concentration of 100 mg Iodine/mL and 50 mL to 600 mL of OMNIPAQUE at a concentration of 50 mg Iodine/mL.

OMNIPAQUE may be diluted with Sterile Water for Injection as indicated in the table below:

To Achieve	Add To	
A Final Concentration	Each 100 mL of OMNIPAQUE Sterile Water for Injection, USP (mL)	
(mg Iodine/mL)	OMNIPAQUE 300	OMNIPAQUE 350
100	200	250
90	233	289
80	275	338
70	330	400
60	400	483
50	500	600

Dilutions of OMNIPAQUE should be prepared just prior to use and any unused portion discarded after the procedure.

ARTHROGRAPHY

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL or OMNIPAQUE 350 at a concentration of 350 mg Iodine/mL is indicated in radiography of the knee joint in adults, and OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is indicated in radiography of the shoulder joint in adults, and OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is indicated in radiography of the temporomandibular joint in adults. Arthrography may be helpful in the diagnosis of posttraumatic or degenerative joint diseases, synovial rupture, the visualization of communicating bursae or cysts, and in meniscography.

Precautions

See PRECAUTIONS—General.

Strict aseptic technique is required to prevent infection. Fluoroscopic control should be used to ensure proper needle placement, prevent extracapsular injection, and prevent dilution of contrast medium. Undue pressure should not be exerted during injection.

Adverse Reactions

Injection of OMNIPAQUE into the joint is associated with transient discomfort, ie, pain, swelling. However, delayed, severe or persistent discomfort may occur occasionally. Severe pain may often result from undue use of pressure or the injection of large volumes. Joint swelling after injection is less with OMNIPAQUE than with high osmolar ionic contrast medium. These types of reactions are generally procedurally dependent and of greater frequency when double-contrast technique is employed.

Nervous system: Swelling sensation (42%), pain (29%), heat sensation (13%), and muscle weakness (0.7%).

Skin and appendages: Hematoma at injection site (0.7%).

Dosage and Administration

Arthrography is usually performed under local anesthesia. The amount of OMNIPAQUE injected is dependent on the size of the joint to be examined and the technique employed. Lower volumes of contrast medium are usually injected for knee and shoulder arthrography when double-contrast examinations using 15 mL to 100 mL of air are performed.

The following concentrations and volumes are recommended for normal adult knee, shoulder, and temporomandibular joints but should serve as guidelines since joints may require more or less contrast medium for optimal visualization.

KNEE
OMNIPAQUE 300 5 mL to 15 mL
OMNIPAQUE 350 5 mL to 10 mL
SHOULDER
OMNIPAQUE 300 10 mL
TEMPOROMANDIBULAR
OMNIPAQUE 300 0.5 mL to 1 mL

} Lower volumes recommended for double-contrast examinations; higher volumes recommended for single-contrast examinations.

Passive or active manipulation is used to disperse the medium throughout the joint space.

HYSTEROSALPINGOGRAPHY

OMNIPAQUE 300 at a concentration of 300 mg Iodine/mL is indicated in radiography of the internal group of adult female reproductive organs; ovaries, fallopian tubes, uterus, and vagina. Hysterosalpingography is utilized as a diagnostic and therapeutic modality in the treatment of infertility and other abnormal gynecological conditions.

Contraindications

OMNIPAQUE 300 for hysterosalpingography is contraindicated during pregnancy or suspected pregnancy, menstruation or when menstruation is imminent, within 6 months after termination of pregnancy, within 30 days after conization or curettage, when signs of infection are present in any portion of the genital tract including the external genitalia, and when reproductive tract neoplasia is known or suspected because of the risk of peritoneal spread of neoplasm.

Adverse Reactions

Injection of OMNIPAQUE for hysterosalpingography is associated with immediate, transient pain. Monitor injection pressure and volume instilled to minimize pain and to avoid disruptive distention of the uterus and fallopian tubes. Fluoroscopic monitoring is recommended.

Nervous system: Pain (49%), somnolence and fever each with an individual incidence of 3%.

Gastrointestinal system: Nausea (3%).

Dosage and Administration

The recommended dosage of OMNIPAQUE 300 is 15 mL to 20 mL but will vary depending on individual anatomy and/or disease state.

DIRECTIONS FOR USE

a. The transfer of OMNIPAQUE (Iohexol Injection) from the Pharmacy Bulk Package is restricted to a suitable work area, such as a laminar flow hood.
b. The container closure may be penetrated only one time, utilizing a suitable transfer device and aseptic technique.
c. The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of 8 hours from initial closure entry is permitted to complete fluid transfer operations. The container should not be removed from the aseptic area during the entire 8 hour period.
d. The temperature of the container should not exceed 37°C, after the closure has been entered.

HOW SUPPLIED

OMNIPAQUE 300
500 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 Pharmacy Bulk Packages
(NDC 0407-1413-68)

OMNIPAQUE 350
500 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 Pharmacy Bulk Packages
(NDC 0407-1414-98)

Protect polymer bottles of OMNIPAQUE from strong daylight and direct exposure to sunlight. Do not freeze. OMNIPAQUE should be stored at controlled room temperature, 20°-25°C (68°- 77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

OMNIPAQUE Injection in all presentations may be stored in a contrast media warmer for up to one month at 37°C (98.6°F).

SPECIAL HANDLING AND STORAGE FOR POLYMER BOTTLES ONLY: DO NOT USE IF TAMPER-EVIDENT RING IS BROKEN OR MISSING.

GE Healthcare

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Revised 2/2022

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OMNIPAQUE IMAGING BULK PACKAGE safely and effectively. See full prescribing information for OMNIPAQUE IMAGING BULK PACKAGE.

OMNIPAQUE (iohexol) injection, for intravenous use
Initial U.S. Approval: 1985

WARNING: RISKS WITH INADVERTANT INTRATHECAL ADMINISTRATION
See full prescribing information for complete boxed warning.

FOR INTRAVENOUS USE ONLY. Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema (5.1).

----------RECENT MAJOR CHANGES ----------
Warnings and Precautions (5.7) 2/2022

----------INDICATIONS AND USAGE----------
OMNIPAQUE Imaging Bulk Package is a radiographic contrast agent indicated for intravenous computed tomographic (CT) imaging of the head and body in adult and pediatric patients. (2.1)

For use only with an automated contrast injection system, contrast management system, or contrast media transfer set cleared for use with OMNIPAQUE Imaging Bulk Package.

----------DOSAGE AND ADMINISTRATION----------
The concentration and volume required will depend on the equipment and imaging technique used. See full prescribing information for full dosing information. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 500 mL Imaging Bulk Package available in two strengths:
- 300 mg of iodine per mL (647 mg of iohexol/mL) and
- 350 mg of iodine per mL (755 mg of iohexol/mL) (3)

----------CONTRAINDICATIONS----------
None

----------WARNINGS AND PRECAUTIONS ----------
- For intravenous use only. (5.1)
- Hypersensitivity Reactions: Life-threatening or fatal reactions can occur. Always have emergency equipment and trained personnel available. (5.2)
- Contrast-Induced Acute Kidney Injury: Acute injury including renal failure can occur. Minimize dose and maintain adequate hydration to minimize risk. (5.3)
- Cardiovascular Adverse Reactions: Hemodynamic disturbances including shock and cardiac arrest may occur during or after administration. (5.4)
- Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age: Monitor these patients for thyroid function abnormalities and treat as clinically needed. (5.7)

----------ADVERSE REACTIONS----------
Most common adverse reactions in adult patients:(incidence > 1%) pain, vision abnormalities (including blurred vision and photomas), headache, taste perversion, arrhythmias including premature ventricular contractions (PVCs) and premature atrial contractions (PACs), angina/chest pain, nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Lactation: A lactating woman may pump and discard breast milk for 10 hours after OMNIPAQUE administration. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: RISKS WITH INADVERTENT INTRATHECAL ADMINISTRATION

FOR INTRAVENOUS USE ONLY. Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

OMNIPAQUE Imaging Bulk Package is indicated for

- Computed tomographic (CT) imaging of the head and body by intravenous administration in:
  - adults (300 and 350 mg iodine/mL)
  - pediatric patients (300 mg iodine/mL)

For use only with an automated contrast injection system, contrast management system, or contrast media transfer set cleared for use with OMNIPAQUE Imaging Bulk Package.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- OMNIPAQUE is for intravenous use only *[see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)]*
- OMNIPAQUE may be administered at body (37°C) or room temperature. Do not warm the container beyond 37°C.
- Inspect OMNIPAQUE for particulate matter or discoloration before administration, whenever solution and container permit. Do not administer if OMNIPAQUE contains particulate matter or is discolored.
- Do not mix OMNIPAQUE with, or inject in intravenous lines containing, other drugs or total nutritional admixtures.
- Use sterile technique for all handling and administration of OMNIPAQUE.
- Hydrate patients before and after OMNIPAQUE administration *[see Warnings and Precautions (5.3)]*.
- Avoid extravasation when injecting OMNIPAQUE, especially in patients with severe arterial or venous disease *[see Warnings and Precautions (5.5)]*

2.2 Recommended Dosage

- The dosing recommendations for OMNIPAQUE Imaging Bulk Package are summarized below for adult (Table 1) and pediatric (Table 2) patients.
- The maximum recommended total dose of iodine for adults is 60 grams.
- Use the lowest dose necessary to obtain adequate visualization.
- Individualize the volume, strength, and rate of administration of OMNIPAQUE Imaging Bulk Package. Consider factors such as age, body weight, vessel size, blood flow rate within the vessel, anticipated pathology, degree and extent of opacification required, structures or area to be examined, disease processes affecting the patient, and equipment and technique to be employed.

Table 1

Adult Dosing Recommendations: Intravenous Administration		
STUDY TYPE	**300 mg iodine/mL**	**350 mg iodine/mL**
CT Imaging – Head	70 to 150 mL (21 to 45 grams iodine)	80 mL (28 grams iodine)
CT Imaging – Body	50 to 200 mL (15 to 60 grams iodine)	60 to 100 mL (21 to 35 grams iodine)

Table 2

Pediatric Patients* Dosing Recommendations: Intravenous Administration		
	STUDY TYPE	**300 mg iodine/mL**
Dosage for infants and children should be administered in proportion to age and body weight.	CT Imaging – Head and Body	1 to 2 mL/kg Maximum single dose = 3mL/kg 35 grams iodine (116 mL)

**The concentration and volume required will depend on the equipment and imaging technique used.*

2.3 Imaging Bulk Package Preparation Instructions

- OMNIPAQUE Imaging Bulk Package is for use only with an automated contrast injection system, contrast management system, or contrast media transfer set cleared for use with this contrast agent in this Imaging Bulk Package. See device labeling for information on devices indicated for use with this Imaging Bulk Package and techniques to help assure safe use.
- Use OMNIPAQUE Imaging Bulk Package and 0.9% Sodium Chloride Injection only in a room designated for radiological procedures that involve intravascular administration of a contrast agent.
- Utilize sterile technique for penetrating the container closure of the OMNIPAQUE Imaging Bulk Package and transferring OMNIPAQUE solution. The container closure may be penetrated only one time with a suitable sterile component of the automated contrast injection system, contrast management system, or contrast media transfer set cleared for use with this Imaging Bulk Package. Do not use if tamper-evident ring is broken or missing.
- If 0.9% Sodium Chloride Injection USP is used, prepare the 0.9% Sodium Chloride Injection USP sterile port in accordance with the dosage and administration section of its approved prescribing information. The intravenous administration port of the 0.9% Sodium Chloride Injection USP container may be penetrated only one time with a suitable sterile component of the contrast management system approved for use with the OMNIPAQUE Imaging Bulk Package.
- Affix the saline tag provided with the OMNIPAQUE Imaging Bulk Package on the 0.9% Sodium Chloride Injection USP container.
- Once the OMNIPAQUE Imaging Bulk Package and 0.9% Sodium Chloride Injection are punctured do not remove them from the work area during the entire period of use. Maintain the OMNIPAQUE Imaging Bulk Package bottle in an inverted position such that container contents are in continuous contact with the dispensing set.
- After the container closure is punctured, if the integrity of the OMNIPAQUE Imaging Bulk Package, the 0.9% Sodium Chloride, and the delivery system cannot be assured through direct continuous supervision, discard the OMNIPAQUE Imaging Bulk Package, 0.9% Sodium Chloride, and all associated disposables for the iodinated contrast media transfer set.
- A maximum time of 8 hours from initial puncture is permitted to complete fluid transfer. Discard any unused OMNIPAQUE solution and 0.9% Sodium Chloride 8 hours after initial puncture of the OMNIPAQUE Imaging Bulk Package.

3 DOSAGE FORMS AND STRENGTHS

Injection: Non-ionic, sterile, pyrogen-free, colorless to pale yellow solution in an imaging bulk package in the following strengths:

- 300 mg of organically bound iodine per mL (647 mg of iohexol/mL)
- 350 mg of organically bound iodine per mL (755 mg of iohexol/mL)

Imaging Bulk Package is available in the following format: 500 mL polymer bottle (*PLUS*PAK™)

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risks with Inadvertent Intrathecal Administration

OMNIPAQUE is for intravenous use *only [see Dosage and Administration (2.1)].* Inadvertent Intrathecal administration can cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

5.2 Hypersensitivity Reactions

OMNIPAQUE, can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Most severe reactions develop shortly after the start of the injection (within 3 minutes), but reactions can occur up to hours later. There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (i.e., bronchial asthma, drug, or food allergies) or other hypersensitivities. Premedication with antihistamines or corticosteroids does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

Obtain a history of allergy, hypersensitivity, or hypersensitivity reactions to iodinated contrast agents and always have emergency resuscitation equipment and trained personnel available prior to OMNIPAQUE administration. Monitor all patients for hypersensitivity reactions.

5.3 Contrast-Induced Acute Kidney Injury

Acute kidney injury, including renal failure, may occur after OMNIPAQUE administration. Risk factors include: pre-existing renal impairment, dehydration, diabetes mellitus, congestive heart failure, advanced vascular disease, elderly age, concomitant use of nephrotoxic or diuretic medications, multiple myeloma/paraproteinaceous diseases, repetitive and/or large doses of an iodinated contrast agent.

Use the lowest necessary dose of OMNIPAQUE in patients with renal impairment. Adequately hydrate patients prior to and following OMNIPAQUE administration. Do not use laxatives, diuretics, or preparatory dehydration prior to OMNIPAQUE administration.

5.4 Cardiovascular Adverse Reactions

Life-threatening or fatal cardiovascular reactions including hypotension, shock, cardiac arrest have occurred with the use of OMNIPAQUE. Based upon clinical literature, reported deaths from the administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 per 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor.

OMNIPAQUE has the potential to transiently increase in the circulatory osmotic load in patients with congestive heart failure. Use the lowest necessary dose of OMNIPAQUE in patients with congestive heart failure and observe these patients for several hours following the procedure to detect delayed hemodynamic disturbances. Monitor all patients for severe cardiovascular reactions always have emergency resuscitation equipment and trained personnel available.

5.5 Extravasation and Injection Site Reactions

Extravasation of intravenously administered OMNIPAQUE may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease. Ensure

intravenous placement of catheters prior to injection. Monitor patients for extravasation and advise patients to seek medical care for progression of symptoms.

5.6 Thyroid Storm in Patients with Hyperthyroidism

Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule. Evaluate the risk in such patients before use of OMNIPAQUE.

5.7 Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age

Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media. Among patients 0 to 3 years of age exposed to iodinated contrast media, thyroid dysfunction has been reported in 1% to 15% depending on the age of the patient and the dose of the iodinated contrast agent.

Younger age, very low birth weight, prematurity, and the presence of other conditions, such as, admission to neonatal or pediatric intensive care units, and cardiac conditions are associated with an increased risk. Pediatric patients with cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures, such as catheterization and computed tomography (CT).

Pediatric patients 0 to 3 years of age warrant closer monitoring because an underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. Evaluate thyroid function in all pediatric patients 0 to 3 years of age within 3 weeks following exposure to iodinated contrast media, especially in term and preterm neonates. If thyroid dysfunction is detected, treat and monitor thyroid function as clinically needed.

5.8 Hypertensive Crisis in Patients with Pheochromocytoma

Hypertensive crisis has occurred after the use of iodinated contrast agents in patients with pheochromocytoma. Monitor patients when administering OMNIPAQUE if pheochromocytoma or catecholamine-secreting paragangliomas are suspected. Inject the minimum amount of contrast necessary, assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.

5.9 Sickle Cell Crisis in Patients with Sickle Cell Disease.

Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease. Hydrate patients prior to and following OMNIPAQUE administration and use OMNIPAQUE only if the necessary imaging information cannot be obtained with alternative imaging modalities.

5.10 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agents; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering OMNIPAQUE to patients with a history of a severe cutaneous adverse reaction to OMNIPAQUE.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks Associated with Inadvertent Intrathecal Administration *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*

- Contrast-Induced Kidney Injury *[see Warnings and Precautions (5.3)]*
- Cardiovascular Adverse Reactions *[see Warnings and Precautions (5.4)]*
- Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age *[see Warnings and Precautions (5.7)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults: The following Adverse Reactions are listed in decreasing frequency within each subgroup. *Cardiovascular System:* arrhythmias including premature ventricular contractions (PVCs) and premature atrial contractions (PACs), angina/chest pain, hypotension, cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction

Nervous System: pain, vision abnormalities (including blurred vision and photomas), headache, taste perversion, vertigo, dizziness, lightheadedness, anxiety, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus.

Respiratory System: dyspnea, rhinitis, coughing, and laryngitis

Gastrointestinal System: nausea, vomiting, diarrhea, dyspepsia, cramp, and dry mouth Skin and Appendages: urticaria, purpura, abscess, and pruritus

Pediatric Patients: In controlled clinical trials involving pediatric patients for CT head imaging, adverse reactions following the use of OMNIPAQUE (300 mg iodine/mL) were similar in quality and frequency to those seen with adults.

6.2 Post-Marketing Experience

The following additional reactions have been identified during post-approval intravascular use of OMNIPAQUE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure.

Hemodynamic Reactions: vein cramp and thrombophlebitis following intravenous injection

Blood and Lymphatic System Disorders: neutropenia

Cardiovascular Disorders: cardiac arrest, shock, peripheral vasodilatation hypertension, myocardial infarction, spasm of coronary arteries, reflex tachycardia, cyanosis, pallor, flushing

Eye Disorders: transient visual impairment including cortical blindness, eyelid edema, conjunctival symptoms, lacrimation

Endocrine Reactions: hyperthyroidism, hypothyroidism

Gastrointestinal Disorders: abdominal pain, pancreatitis aggravated, salivary gland enlargement

General Disorders and Administration Site Conditions: chills, pyrexia, pain and discomfort, weakness, administration site conditions including extravasation, feeling hot

Immune System Disorders: hypersensitivity reactions, anaphylactic or anaphylactoid shock including life-threatening or fatal anaphylaxis

Musculoskeletal and Connective Tissue Disorders: back pain

Nervous System Disorders: coma, disturbance in consciousness, transient contrast-induced encephalopathy caused by extravasation of contrast media (including amnesia, hallucination, paralysis, paresis, speech disorder, aphasia, dysarthria), restlessness, tremors, hypoesthesia

Psychiatric Disorders: confusional state, agitation

Renal Disorders: acute kidney injury, nephropathy toxic, transient proteinuria, oliguria or anuria, increased

serum creatinine

Respiratory; Thoracic, and Mediastinal Disorders: respiratory arrest, pulmonary or laryngeal edema, bronchospasm, sneezing, throat irritation, throat tightness, laryngeal edema, pharyngeal edema, asthmatic attack

Skin and Subcutaneous Tissue Disorders: Reactions range from mild (e.g., pleomorphic rashes, drug eruption, erythema, pruritus, urticaria and skin discoloration, hyperhidrosis, angioedema, localized areas of edema) to severe: [e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)]

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

Metformin
In patients with renal impairment, metformin can cause lactic acidosis. Iodinated contrast agents appear to increase the risk of metformin-induced lactic acidosis, possibly as a result of worsening renal function. Stop metformin at the time of, or prior to, OMNIPAQUE administration in patients with an estimated Glomerular Filtration Rate (eGFR) between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and reinstitute metformin only after renal function is stable.

Radioactive Iodine
Administration of iodinated contrast agents may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy in patients with carcinoma of the thyroid. The decrease in efficacy lasts for 6 to 8 weeks.

Beta-adrenergic Blocking Agents
The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and reduces the responsiveness of treatment of hypersensitivity reactions with epinephrine. Because of the risk of hypersensitivity reactions, use caution when administering OMNIPAQUE to patients taking beta-blockers.

7.2 Drug Laboratory Test Interactions

Effect on Thyroid Tests
If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast agent administration. Thyroid function tests which do not depend on iodine estimation, e.g., T_3 resin uptake or direct thyroxine assays, are not affected.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Postmarketing data with OMNIPAQUE use in pregnant women are insufficient to determine if there is a drug-associated risk of adverse developmental outcomes. Iohexol crosses the placenta and reaches fetal tissues in small amounts *(see Data).* In animal reproduction studies, no adverse developmental effects were observed following intravenous iohexol administration to pregnant rats and rabbits during organogenesis at doses up to 0.4 (rat) and 0.5 (rabbit) times the maximum recommended human intravenous dose *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically

recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Literature reports show that iohexol crosses the placenta and is visualized in the digestive tract of exposed infants after birth.

Animal Data

Reproduction studies were performed in rats and rabbits with intravenous administration of iohexol at the following dose levels: 1.0, 2.0, 4.0 g iodine/kg in rats, in 3 groups of 25 dams once daily during days 6 through 15 of pregnancy; 0.3, 1.0, 2.5 g iodine/kg in rabbits, in 3 groups of 18 doses once a day during days 6 through 18 of pregnancy. Iohexol was not embryotoxic or teratogenic in either species at the dose levels tested.

8.2 Lactation

Risk Summary

The literature reports that breast feeding after iohexol administration to the mother would result in the infant receiving an oral dose of approximately 0.7% of the maternal intravenous dose. There is no information on the effects of the drug on milk production. Iodinated contrast agents are excreted unchanged in human milk in very low amounts with poor absorption from the gastrointestinal tract of a breastfed infant. Exposure to iohexol to a breastfed infant can be minimized by temporary discontinuation of breastfeeding *(see Clinical Considerations).* The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OMNIPAQUE and any potential adverse effects on the breastfed infant from OMNIPAQUE or from the underlying maternal condition.

Clinical Considerations

Interruption of breastfeeding after exposure to iodinated contrast agents is not necessary because the potential exposure of the breastfed infant to iodine is small. However, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 elimination half-lives) after OMNIPAQUE administration to minimize drug exposure to a breastfed infant.

8.4 Pediatric Use

The safety and efficacy of OMNIPAQUE 300 mg iodine/mL have been established in pediatric patients birth to 17 years of age for CT imaging of the head and body. Use of OMNIPAQUE 300 mg iodine/mL is supported by controlled clinical trials in pediatric patients undergoing head CT and evidence of effectiveness from well-controlled studies of OMNIPAQUE in adults for head and body CT. The safety and efficacy of OMNIPAQUE 350 mg iodine/mL have not been established in pediatric patients birth to 17 years of age for CT imaging of the head and body.

In general, the frequency of adverse reactions in pediatric patients was similar to that seen in adults *[see Adverse Reactions (6.1)]*. Pediatric patients at higher risk of experiencing adverse events during contrast agent administration may include those having asthma, sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

Thyroid function tests indicative of thyroid dysfunction, characterized by hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration in pediatric patients, including term and preterm neonates. Some patients were treated for hypothyroidism. Monitor pediatric patients 0 to 3 years of age closely, particularly those with one or more potential risk factors, for thyroid dysfunction *[see Warnings and Precautions (5.7) and Adverse Reactions (6.2)]*.

8.5 Geriatric Use

In clinical studies of OMNIPAQUE in computed tomography, 52/299 (17%) of patients were 70 years and

older. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

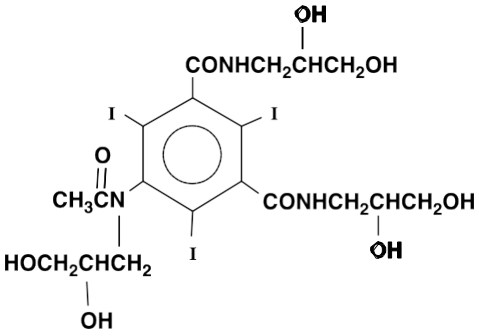
10 OVERDOSAGE

The adverse reactions to overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy. Iohexol displays a low affinity for serum or plasma proteins and is poorly bound to serum albumin and, therefore, can be dialyzed.

11 DESCRIPTION

11.1 Chemical Characteristics

OMNIPAQUE (iohexol) is a nonionic, radiographic contrast agent for intravenous use. OMNIPAQUE is provided as a sterile, pyrogen-free, colorless to pale-yellow solution. The chemical name of iohexol is Bis(2,3-dihydroxypropyl)-5-[*N*- (2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodoisophthalamide with a molecular weight of 821.14 (iodine content 46.36%). Iohexol has the following structural formula:



- OMNIPAQUE 300 mg iodine/mL (647 mg of iohexol/mL): Each mL contains 300 mg organically bound iodine, 1.21 mg tromethamine, 0.1 mg edetate calcium disodium
- OMNIPAQUE 350 mg iodine/mL (755 mg of iohexol/mL): Each mL contains 350 mg organically bound iodine, 1.21 mg tromethamine, 0.1 mg edetate calcium disodium

The pH is adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. All solutions are sterile and contain no preservatives.

11.2 Physical Characteristics

Table 3 summarizes the physical properties of the two concentrations of OMNIPAQUE Imaging Bulk Package.

TABLE 3

Concentration (mg iodine/mL)	Osmolality* (mOsm/kg water)	Absolute Viscosity (cp)		Specific Gravity
		20°C	37°C	37°C

300	672	11.8	6.3	1.349
350	844	20.4	10.4	1.406
* By vapor-pressure osmometry.				

OMNIPAQUE 300 mg iodine/mL and OMNIPAQUE 350 mg iodine/mL have osmolalities from approximately 2.2 to 3 times those of plasma (285 mOsm/kg water) or cerebrospinal fluid (301 mOsm/kg water) and are hypertonic under conditions of use.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Intravascular injection of iohexol opacifies vessels in the path of flow through attenuation of X-rays permitting visualization of the internal structures.

Iohexol diffuses from the vascular into the extravascular space. Vessels feeding tumors are less of a barrier to iohexol diffusion than are normal vessels, resulting in increased accumulation in the extravascular space around tumors and thus contrast enhancement. However, iohexol does not accumulate in normal brain tissue due to the presence of the intact blood-brain barrier. A disruption in the blood-brain barrier allows for the accumulation of contrast agent within the interstitial space in the region of disruption.

12.2 Pharmacodynamics

Following administration of OMNIPAQUE, the degree of contrast enhancement is directly related to the iodine content in an administered dose; peak iodine blood concentrations occur immediately following rapid intravenous injection. The time to maximum contrast enhancement can vary, depending on the organ, from the time that peak blood iodine concentrations are reached to one hour after intravenous bolus administration. When a delay between peak blood iodine concentrations and peak contrast is present, it suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine containing agent within the lesion and outside the blood pool.

Renal accumulation is sufficiently rapid that the period of maximal opacification of the renal collecting system may begin as early as 1 minute after intravenous injection. Urograms become apparent in about 1 to 3 minutes with optimal contrast occurring between 5 to 15 minutes.

12.3 Pharmacokinetics

Following the intravenous administration of iohexol (between 500 mg iodine/kg to 1500 mg iodine/kg) to 16 adult human subjects, apparent first-order terminal elimination half-life was 12.6 hrs and total body clearance was 131 (98 to 165) mL/min. Clearance does not appear to be dose dependent.

Distribution

In 16 adult subjects (receiving between 500 mg iodine/kg to 1500 mg iodine/kg intravenous iohexol) the volume of distribution was 165 (108 to 219) mL/kg.

Elimination

Metabolism
No significant metabolism, deiodination or biotransformation occurs.

Excretion
Following intravascular injection, iohexol is excreted unchanged by glomerular filtration. 90% or more of the injected iohexol dose is excreted within the first 24 hours, with the peak urine concentrations occurring in the first hour after administration.

Specific Populations

Renal Impairment
In patients with renal impairment, greater plasma iohexol exposure may be anticipated due to slowed elimination of iohexol. In these patients, as well as in infants with immature kidneys, fecal excretion of iohexol may occur.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed with iohexol to evaluate carcinogenic potential. Iohexol was not genotoxic by the Ames test, the mouse lymphoma TK locus forward mutation assay, and a mouse micronucleus assay. Iohexol did not impair the fertility of male or female rats when repeatedly administered at intravenous dosages up to 4 g iodine/kg.

14 CLINICAL STUDIES

14.1 Intravenous Administration Studies

OMNIPAQUE Clinical Studies for CT
The safety and efficacy of intravenously administered OMNIPAQUE for CT of the head and body were evaluated in six clinical studies (Table 4). Each study also used an ionic high-osmolar iodinated contrast agent as a comparator (Table 4). Patients were randomized to administration of either OMNIPAQUE or the comparator. OMNIPAQUE patients had a mean age of 53 years (range 16 to 85), were 44% women, had a mean weight of 67 kg (range 36 to 134), and were administered a mean of 572 mg iodine/kg (range 176 to 1250); comparator patients had a mean age of 51 years (range 14 to 80), were 43% women, had a mean weight of 70 kg (range 40 to 136), and were administered a mean of 484 mg iodine/kg (range 135 to 1500). In three studies, efficacy was determined from investigator ratings of quality of contrast enhancement (none, poor, good, or excellent; only scans rated as good or excellent were considered diagnostic); in the remaining three studies, efficacy was assessed quantitatively through X-ray attenuation, measured pre-contrast and at various time points post-contrast.

The percentage of scans rated as good or excellent was 100% for both OMNIPAQUE and the comparator in each of the two studies, and 79% for OMNIPAQUE and 74% for the comparator in the third study. In the studies that measured X-ray attenuation, there were no clinically significant differences between OMNIPAQUE and the comparator regarding contrast over time or time to maximal attenuation.

Overall, the incidence of discomfort (heat, pain, cold, tingling, pressure, chest heaviness, or cramp) was lower in the patients receiving OMNIPAQUE, with 115 (38%) of 300 patients receiving OMNIPAQUE vs. 177 (60%) of 295 comparator patients reporting discomfort ionic media ($p<0.001$). Similarly, fewer patients receiving OMNIPAQUE than comparator patients reported adverse events (7% versus 19%, respectively, $p<0.001$).

Table 4

Study	Indication	OMNIPAQUE (mg iodine/mL)	No. of Patients Receiving OMNIPAQUE	Comparator (mg iodine/mL)	Patients Receiving Comparator
1	Intracranial	300	26	Diatrizoate (282)	23
2		300	16	Iothalamate (282)	15
3		350	30	Metrizoate (350)	30
4		240	100	Diatrizoate (168)	100
5	Abdominal	350	28	Metrizoate (350)	27
6		300	100	Metrizoate (280)	100
TOTAL			**300**		**295**

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

OMNIPAQUE injection is provided as a sterile, pyrogen-free, preservative free, colorless-to-pale yellow solution available in two strengths in an Imaging Bulk Package. It is supplied in the following configurations:

OMNIPAQUE Imaging Bulk Package (iohexol) Injection 300 mg iodine/mL:
500 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 Imaging Bulk Packages (NDC 0407-1413-72)

OMNIPAQUE Imaging Bulk Package (iohexol) Injection 350 mg iodine/mL:
500 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10 Imaging Bulk Packages (NDC 0407-1414-72)

16.2 Storage and Handling

Protect OMNIPAQUE Imaging Bulk Package from exposure to sunlight.

Store OMNIPAQUE Imaging Bulk Package at controlled room temperature, 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. OMNIPAQUE Imaging Bulk Package may be stored in a contrast media warmer for up to one month at 37°C (98.6°F).

Do not freeze. Discard any product that is inadvertently frozen, as freezing may compromise the closure integrity of the immediate container.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions
Advise the patient concerning the risk of hypersensitivity reactions that can occur both during and after OMNIPAQUE administration. Advise the patient to report any signs or symptoms of hypersensitivity reactions during the procedure and to seek immediate medical attention for any signs or symptoms experienced after discharge *[see Warnings and Precautions (5.2)]*

Advise patients to inform their physician if they develop a rash after receiving OMNIPAQUE *[see Warnings and Precautions (5.10)]*.

Contrast-Induced Acute Kidney Injury
Advise the patient concerning appropriate hydration to decrease the risk of contrast-induced acute kidney injury *[see Warnings and Precautions (5.3)]*.

Extravasation
If extravasation occurs during injection, advise patients to seek medical care for progression of symptoms *[see Warnings and Precautions (5.5)]*.

Lactation

Advise a lactating woman that interruption of breastfeeding is not necessary, however, to avoid any exposure a lactating woman may consider pumping and discarding breast milk for 10 hours after OMNIPAQUE administration *[see Use in Specific Populations (8.2)]*.

Thyroid Dysfunction

Advise parents/caregivers about the risk of developing thyroid dysfunction after OMNIPAQUE administration. Advise parents/caregivers about when to seek medical care for their child to monitor for thyroid function *[see Warnings and Precautions (5.7)]*.

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