New Zealand Datasheet

1 PRODUCT NAME
OMNIPAQUE™

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Iohexol240, 300 and 350 mg iodine per ml.

3 PHARMACEUTICAL FORM
240 mg, bottles containing 518 mg iohexol per ml, equivalent to 240 mg Iodine per ml.
300 mg, bottles containing 647 mg iohexol per ml, equivalent to 300 mg iodine per ml.
350 mg, bottles containing 755 mg iohexol per ml, equivalent to 350 mg iodine per ml.

OMNIPAQUE solutions are colourless.

The osmolality and viscosity values are as follows:

Concentration (mg I/ml)	Osmolality* (mol/kg)	Viscosity (mPa s) 20ºC	Viscosity (mPa s) 37ºC
240	0.51	5.6	3.3
300	0.64	11.6	6.1
350	0.78	23.3	10.6

* at 37ºC, in aqueous solutions of iohexol.

OMNIPAQUE is isotonic to blood (300 mOsm/kg) and cerebrospinal fluid (CSF) at a concentration of 140 mg I/ml. The density of OMNIPAQUE at the available concentrations is hyperbaric to CSF.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
This medicinal product is for diagnostic use only.

Intravscular
OMNIPAQUE is indicated in adults for angiography, excretory urographyand CT-enhancement. In children, OMNIPAQUE is indicated for angiography and urography.

Intrathecal
OMNIPAQUE is indicated for lumbar, thoracic, cervical and total columnar myelography and computed tomography of the CNS in adults and children.

Oral/Body cavities
OMNIPAQUE is indicated in adults in arthrography, endoscopic retrograde pancreatography (ERP), endoscopic retrograde cholangiopancreatography (ERCP), herniography, hysterosalpingography, and in adults, children and prematurte babies for studies of the gastrointestinal tract.

4.2 Dose and method of administration

Administration of contrast media should be performed by qualified personnel familiar with the procedure, and an appropriate technique should be utilised.

The dosage varies depending on the type of examination, age, weight, cardiac output and general condition of the patient and the technique used. Adequate hydration should be assured before and after administration as for other contrast media.

As in all diagnostic procedures, the lowest dose of OMNIPAQUE necessary to obtain adequate visualisation should be used. 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 individualised 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 process affecting the patient, and equipment and technique to be employed should be considered.

Patients will tolerate a contrast medium better if the contrast medium is warmed to body temperature, which lowers the viscosity.

OMNIPAQUE should be inspected visually for particulate matter, discolouration and the integrity of the container prior to administration. OMNIPAQUE should only be used if clear and within the normal colourless to pale yellow range. Do not use if particulate matter or discolouration are present.

The following dosages may serve as a guide.

Guidelines for Intravascular use

Indication	Volume	Concentration	Route of Administration
Urography - Adults - Children < 7 kg - Children > 7 kg	 Usual dose 200 mg I/kg Max dose 400 mg I/kg **(40-80 mL, 80 mL may be exceeded in selected cases)** Up to 3 mL/kg Up to 2mL/kg (Max. 40mL)	 300 mg I/mL or 350 mg I/mL 300 mg I/mL	Intravenous
Cerebral angiography	5-10 mL/inj	300 mg I/mL	Intra-arterial
Cardioangiography - Adults **Left ventricular and aortic root injections** - Children Selective coronary arteriography	 45-60 mL total 1-2 mL/kg inj (2-6 mL/kg total) 1.5-8 mL/inj	 350 mg I/mL 300 mg I/mL 350 mg I/mL	Intra-arterial
Peripheral arteriography	30-80 mL total	300 mg I/mL	Intra-arterial
Visceral angiography	5-45 mL selective	300 mg I/mL or 350 mg I/mL	Intra-arterial
Phlebography	30-50 mL/leg/inj	240 mg I/mL or 300 mg I/mL	Intravenous
Contrast-enhanced computer tomography - Cerebral - Abdominal	 1.5 mL/kg (up to 100 mL total) 80 mL 60 mL	 300 mg I/mL 350 mg I/mL 350 mg I/mL	 Intravenous Intravenous
Digital subtraction angiography	30-50 mL/inj Max. 250 mL total	350 mg I/mL	Intravenous

Guidelines for Intrathecal use

To minimise possible adverse reactions a total dose of 3 g iodine should not be exceeded. As in all diagnostic procedures, the minimum concentration and volume to produce adequate visualisation should be used.

To avoid excessive mixing with CSF and consequent dilution of contrast, as well as premature dispersion upwards, injection must be made slowly. Depending on the estimated volume of OMNIPAQUE which may be required for the procedure, a small amount of CSF may be removed to minimise the distension of the subarachnoid spaces.

The needle may be removed immediately following injection since it is not necessary to remove OMNIPAQUE after injection into the subarachnoid space. An interval of 48 hours should be allowed before repeat examination.

Direct intracisternal or ventricular administration for standard radiography (without computerized tomographic enhancement) is not recommended.

Adults
The usual recommended total doses of OMNIPAQUE are:

Procedure	**Concentration (mg I/mL)**	*Volume* **(mL)**
Lumbar myelography	180	8-17
Thoracic myelography	240	7-10
Cervical or total columnar myelography (*via* lumbar puncture)	300	6-10
Cervical myelography (via lateral cervical injection)	240 or 300	8-10 5-10

Infants and Children

OMNIPAQUE 180 mg I/mL is recommended for the examination of the lumbar, thoracic and cervical regions in children by lumbar injection and is slightly hypertonic to CSF. The usual recommended total doses for myelography (by lumbar injection) are given below, depending largely on patient age.

Age	**Concentration (mg I/mL)**	**Volume (mL)**
3-36 months	180	4-8
3-7 years	180	5-10
7-13 years	180	5-12
13-18 years	180	6-15

Avoid rapid dispersion of the medium. (To avoid excessive mixing with cerebrospinal fluid (CSF) and consequent dilution of iohexol solution, injection should be made slowly over 1 to 2 minutes.)

If repeat examinations are desired, a suitable interval of time between administrations is needed 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, 5 to 7 days is recommended whenever possible.

Guidelines for Body Cavities/Oral Use:

Indication	Volume	Concentration	Route of Administration
Arthrography Adults:	 5-20 mL 5-15 mL 5-10 mL (See Administration Instructions #1)	 240 mg I/mL or 300 mg I/mL 350 mg I/mL	 Intra-articular Intrasynovial
ERP/ERCP Adults	 20-50 mL*	 240 mg I/mL	 Intracavitary
Herniography Adults	 50 mL*	 240 mg I/mL	 Intraperitoneal
Hysterosalpingo-graphy Adults	 15-20 mL* 15-20 mL*	 240 mg I/mL 300 mg I/mL	 Intraperitoneal Intrauterine
Gastrointestinal Studies **Oral Use:** Adults -oral pass-through Children: -oesophagus -oral pass-through Prematures **Rectal Use:** Children	 Individual Individual (See Administration Instructions #2) Undiluted: 50-100 mL 2-4 mL/ kg b.w. 2-4 mL/kg b.w. (Max. dose 50 mL) Undiluted: Based on nature of examination and patient size. (See Administration Instructions #3) 2-4 mL/kg b.w. 5-10 mL/kg b.w.	 180 mg I/mL or 300 mg I/mL 350 mg I/mL 300 mg I/mL or 350 mg I/mL 180 mg I/mL (children of all ages including < 3 months of age) 240 mg I/mL (> 3 months of age) 300 mg I/mL (>3 months of age) 180 mg I/mL Eg. Dilute 240, 300 or 350 mg I/mL with tap water to 100-150 mg I/mL	 Oral Rectal
CT-enhancement **Oral Use:** Adults Children **Rectal Use:** Children	 800 - 1000mL of the diluted solution over a period of time. 15-20 mL/kg b.w. of the diluted solution to a maximum volume of 750mL Individual	 E.g. Dilute Omnipaque 300 or 350 mg I/mL with tap water 1:50, to ~ 6 mg I/mL. 180 mg I/mL; 240 mg I/mL 300 mg I/mL Dilute to ~ 6 mg I/mL with tap water.	 Oral Rectal

*Dosage may vary depending on individual anatomy and/or disease state.

Administration Instructions for Body Cavities/Oral Use

1) Arthrography

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 visualisation.

Knee	
Omnipaque 240	5 mL to 15 mL
Omnipaque 300	5 mL to 15 mL
Omnipaque 350	5 mL to 10 mL
Shoulder	
Omnipaque 300	10 mL
Omnipaque 240	3 mL
Temporomandibular	
Omnipaque 300	0.5 mL to 1.0 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.

2) Oral Use

Adults:

The recommended dosage of undiluted Omnipaque 350 at a concentration of 350 mg I/mL for oral pass-through 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.

OMNIPAQUE diluted to concentrations from 6 mg I/mL to 9 mg I/mL and administered orally in conjunction with OMNIPAQUE 300 at a concentration of 300 mg I/mL administered intravenously is 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.

The recommended oral dosage of OMNIPAQUE dilute to concentrations of 6 mg I/mL to 9 mg I/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. In conjunction with dilute oral administration, the recommended dosage of OMNIPAQUE 300 administered 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.

Children:

The dosage of undiluted OMNIPAQUE 300 at a concentration of 300 mg I/mL, OMNIPAQUE

240 at a concentration of 240 mg I/mL or OMNIPAQUE 180 at a concentration of 180 mg I/mL for oral pass-through examination of the gastrointestinal tract is dependent on the nature of the examination and the size of the patient. Based on clinical experience, it is recommended that OMNIPAQUE 180 be used in children less than 3 months of age. OMNIPAQUE 180, OMNIPAQUE 240 or OMNIPAQUE 300 may be used in children 3 months of age and older. The recommended does for oral use in children is 2-4mL/kg. The estimated total volumes based on this dosage are:

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.

OMNIPAQUE diluted to concentrations from 9-21 mg I/mL administered orally in conjunction with OMNIPAQUE 240 at a concentration of 240 mg I/mL or OMNIPAQUE 300 at a concentration of or 300 mg I/mL administered intravenously is indicated in children for use in contrast enhanced computed tomography of the abdomen. The recommended dose is 15-20 mL/kg up to a maximum volume of 750 mL. Smaller administered volumes are needed as the concentration of the final solution is increased. The total oral dose in grams of iodine should generally not exceed 5 g for children less than 3 years of age and 10 g for children 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 consuming the required volume.

In conjunction with dilute oral administration the recommended dosage of OMNIPAQUE 240 and OMNIPAQUE 300 is 2.0 mL/kg when administered intravenously with a range of 1.0 mL/kg to 2.0 mL/kg. Dosage for infants and children 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

History of serious reaction to OMNIPAQUE.

Iodine-containing radiographic contrast media, whether ionic or non-ionic, should not be administered to patients with thyrotoxicosis, anuria or decompensated cardiac insufficiency. These agents are also contraindicated in certain specific procedures and situations such as carotid angiography during the progressive period of stroke; coronary arteriography in the first 4 weeks after myocardial infarction; and the presence of infection or open injury in or near the region to be examined.

Hysterosalpingography
The procedure should not be performed during the menstrual flow or when menstrual flow is imminent, nor should it be performed if infection is present in any portion of the genital tract, including the external genitalia. The procedure is contraindicated in pregnant women or for those in whom pregnancy is suspected. Its use is not advised for 6 months after termination of pregnancy or 30 days after conization or curettage.

Administration technique
Do not administer with intrathecal corticosteroids.

Immediate repeat myelography, in the event of technical failure, is contraindicated because of overdosage considerations (see interval recommendation in section 4.2).

4.4 Special warnings and precautions for use

Hydration

Adequate hydration should be assured before and after contrast media administration. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction, as well as to infants, small children and elderly patients. Young infants (age < 1 year) and especially neonates are susceptible to electrolyte disturbance and haemodynamic alterations.

Preventive measures include:

- Identification of high-risk patients
- Ensuring adequate hydration. If necessary, by maintaining an i.v. infusion from before the procedure until the contrast medium has been cleared by the kidneys.
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, or major surgery, until the contrast medium has been cleared.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

Risk-benefit should be considered when the following medical problems exist:

Hypersensitivty to iohexol:

A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H_1 and H_2 antagonists might be considered in these cases.

The possibility of hypersensitivity including serious life-threatening fatal anaphylactic/anaphylactoid reactions should always be considered. A course of action should therefore be planned in advance, with necessary drugs and equipment available for immediate treatment, should a serious reaction occur. It is advisable always to use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.

Patients using beta-adrenergic blocking agents, particularly asthmatic patients, may have a lower threshold for bronchospasm and are less responsive to treatment with beta agonists and adrenaline, which may necessitate the use of higher doses. These patients may also present with atypical symptoms of anaphylaxis which may be misinterpreted as vagal reaction.

Contrast-medium induced nephrotoxicity:

Contrast medium induced nephrotoxicity is a condition in which impaired renal function (an increase in serum creatinine by more than 25% or 44 µmol/l) occurs within three days following the intravascular administration of a contrast medium in the absence of an alternative aetiology. Dialysis has been used in the prevention of contrast medium induced nephropathy.

Prevention of nephropathy – haemodialysis:

Patients on haemodialysis may receive contrast media for radiological procedures. If clinically indicated, haemodialysis is an effective method for eliminating iodinated contrast medium from

the body. Correlation of the time of contrast media injection with the haemodialysis session is unnecessary, because there is no evidence that haemodialysis protects patients with impaired renal function from contrast medium induced nephropathy. The patient should not be re-exposed to contrast media before the kidney function has returned to its previous function. If contrast medium is to be given again, the patient must be adequately hydrated.

Use in renal impairment
Use of iodinated contrast media may cause increase in serum creatinine and acute kidney injury. To prevent acute kidney injury following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk. Additional concerns are dehydration, poor renal perfusion and the presence of other factors that may be nephrotoxic such as certain medications or major surgery.

Intravascular contrast studies with iodinated contrast media can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Patients with eGFR equal or greater than 60mL/min/1.73m2(CKD 1 and 2) can continue to take metformin normally.

(1) Patients with eGFR 30-59mL/min/1.73m^2 (CKD 3)
Patients receiving intravenous contrast medium with eGRF equal or greater than 45 mL/min/1.73m^2 can continue to take metformin normally
In patients receiving intra-arterial contrast medium and those receiving intravenous contrast medium with an eGFR between 30 and 44mL/min/1.73m^2 metformin should be discontinued 48 hours before contrast medium and should only be restarted 48 hours after contrast medium if renal function has not deteriorated.
(2) In patients with eGFR less than 30mL/min/1.73m^2 (CDK 4 and 5) or with an intercurrent illness causing reduced liver function or hypoxia, metformin is contraindicated. Iodinated contrast media should be avoided.

(3) In emergency cases where renal function is abnormal or unknown, the physician should evaluate the risk / benefit of the contrast medium examination, and precautions should be implemented: Metformin should be stopped, patient hydrated, renal function monitored and patient observed for symptoms of lactic acidosis. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.

Use in hepatic impairment:
A potential risk of transient hepatic dysfunction exists. Particular care is required in patients with severe disturbance of both renal and hepatic function, as they may have significantly delayed contrast medium clearance.

<u>Severe cardiovascular disease or congestive heart failure</u>
Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias.

<u>History of seizures</u>
Patients with acute cerebral pathology, tumours or a history of epilepsy are predisposed for seizures and merit particular care. Also, alcoholics and drug addicts have an increased risk for seizures and neurological reactions.

Intrathecal use.
A few patients have experienced a temporary hearing loss or even deafness after myelography, which is believed to be due to a drop in spinal fluid pressure by the lumbar puncture per se. This also applies to elderly patients who are at increased risk of cerebral pathology. Routine care after myelography should include supine position with head up for a while. Discontinue medications that may lower the seizure threshold at least 48 hours before iohexol administration and do not resume for at least 24 hours post-procedure. Patients on anticonvulsant medication should be maintained on that therapy.

Severe thyrotoxicosis:
Iodinated contrast media should not be administered to patients with thyrotoxicosis (see section 4.3). Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goitre may be at risk of developing hyperthyroidism following injection of iodinated contrast media. One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media.

Multiple myeloma:
Patients with paraproteinemias (myelomatosis and Waldenström's macroglobulinemia) are also at risk.

Known or suspected pheochromocytoma:
The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis. In patients with phaeochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis.

Use in the elderly
No data available

Paediatric Use:
Infants - Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of thyroid stimulating hormone (TSH) were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or more than a month.

Special attention should be paid to paediatric patients below 3 years of age because an incident underactive thyroid during early life may be harmful for motor, hearing, and cognitive development and may require transient T4 replacement therapy. The incidence of hypothyroidism in patients younger than 3 years of age exposed to iodinated contrast media has been reported between 1.3% and 15% depending on the age of the subjects and the dose of the iodinated contrast agent and is more commonly observed in neonates and premature infants. Neonates may also be exposed through the mother during pregnancy. Thyroid function should be evaluated in all paediatric patients younger than 3 years of age following exposure to iodinated contrast media. If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalized.

CNS
Encephalopathy has been reported with the use of contrast media, such as iohexol (see section 4.8). Contrast encephalopathy may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema. Symptoms usually occur within minutes to hours after administration of iohexol, and generally resolve within days.

Factors which increase blood-brain barrier permeability will ease the transfer of contrast media to brain tissue and may lead to possible CNS reactions for instance encephalopathy.

If contrast encephalopathy is suspected, administration of iohexol should be discontinued and appropriate medical management should be initiated.

Precautions related to administration technique:
Risk of procedure-related thrombosis and embolism:
Non-ionic contrast media have less effect on the coagulation system *in vitro*, compared to ionic contrast media. Serious, rarely fatal thromboembolic events causing myocardial infarction and stroke have been reported during angiocardiographic procedures with both ionic and non-ionic contrast media. When performing vascular catheterisation procedures, one should pay meticulous attention to the angiographic technique and flush the catheter frequently (e.g.: with heparinised saline) so as to minimise the risk of procedure-related thrombosis and embolism.

Extravasation:
Extravasation of contrast media may on rare occasions give rise to local pain, and oedema, which usually recedes without sequelae. However, inflammation and even tissue necrosis have been seen. Elevating and cooling the affected site is recommended as routine measures. Surgical decompression may be necessary in cases of compartment syndrome.

Observation-time:
After contrast medium administration the patient should be observed for at least 30 minutes, since the majority of serious side effects occurs within this time. However, delayed reactions, (that is 1 hour or more after application) may occur.

Intrathecal use
Following myelography the patient should rest with the head and thorax elevated by 20º for one hour. Thereafter he/she may ambulate carefully but bending down must be avoided. The head and thorax should be kept elevated for the first 6 hours if remaining in bed. Patients suspected of having a low seizure threshold should be observed during this period.

Outpatients should not be completely alone for the first 24 hours. It is advisable that patients do not drive vehicles or use machinery during the 24 hours following intrathecal examination.

Care is required in patient management to prevent inadvertent intracranial entry of a large bolus dose of the contrast medium. Prophylactic anti-convulsant treatment should be considered in patients with evidence of inadvertent intracranial entry of a large bolus of the medium, since there is an increased risk of seizure in such cases.

Other
Other precautions which apply to the various radiographic contrast medium procedures are the same for OMNIPAQUE as they are for all other non-ionic contrast media. The risk of the procedure itself should be carefully evaluated in each patient. Such precautions include:

Vascular, oral and body cavity use.

Cerebral angiography

- Use with caution in patients with extreme senility, advanced atherosclerosis, or severe hypotension.
- The procedure may be hazardous in subarachnoid haemorrhage and in migraine (because of ischaemic complications).

Peripheral angiography
- Pulsation should be present in the artery to be injected.
- In thromboangiitis obliterans (Buerger's Disease) or ischaemia associated with ascending infection, angiography should be performed with extreme caution, if at all.

Cardioangiography
- Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly since it may induce serious arrhythmias.
- Caution is advised with dosage in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of the haemodynamic changes which may occur after injection into the right heart outflow tract.

Urography
- It is advisable to allow an interval of at least 48 hours before repeating excretory urography.
- Dehydration should be avoided in the elderly, particularly those with polyuria, oliguria, advanced vascular disease or pre-existing dehydration.
- Myelomatosis (see section 4.4).

Arthrography
- 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.

Hysterosalpingography
- In patients with carcinoma or in those in whom the condition is suspected, use caution to avoid possible spreading of the lesion by the procedure.

Effects on laboratory tests
All iodinated contrast media may interfere with tests on thyroid function, thus the iodine-binding capacity of the thyroid may be reduced for up to several weeks.

High concentrations of contrast media in serum and urine can interfere with laboratory tests for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium and phosphate). These substances should therefore not be assayed on the day of examination.

4.5 Interaction with other medicines and other forms of interaction

Use of contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking metformin (see section 4.4).

Patients treated with interleukin-2 less than two weeks previously have been associated with an increased risk for delayed reactions (flu-like symptoms or skin reactions).

Patients using beta blockers may present with atypical symptoms of anaphylaxis which may be misinterpreted as a vagal reaction. The use of beta-adrenergic blocking agents may lower the threshold for bronchospasm in asthmatic patients after contrast medium administration and reduce the responsiveness of treatment with adrenaline.

All iodinated contrast media may interfere with tests on thyroid function, thus the iodine binding capacity of the thyroid may be reduced for up to several weeks.

High concentrations of contrast media in serum and urine can interfere with laboratory tests for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium and phosphate). These substances should therefore not be assayed on the day of examination.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of OMNIPAQUE for use in human pregnancy has not been established. Teratogenicity studies have been performed in rats and rabbits at doses up to 4 g I/kg and 2.5 g I/kg, respectively. No evidence of harm to the embryo or foetus or of impaired fertility has been demonstrated due to OMNIPAQUE.

Since whenever possible, radiation exposure should be avoided during pregnancy, the benefits of an X-ray examination, with or without contrast media, should be carefully weighed against the possible risk. OMNIPAQUE should not be used in pregnancy unless the benefit outweighs the risk and it is considered essential by the physician.

Breast feeding

Approximately 0.5% of the weight adjusted maternal dose is excreted in breast milk during 24 hours after injection of iohexol. Nursing may be continued normally when iodinated contrast media are given to the mother.

4.7 Effects on ability to drive and use machines

It is not advisable to drive a car or use machines during the first 24 hours following intrathecal examination.

4.8 Undesirable effects

General (applies to all uses of iodinated contrast media):

Below are listed possible general side effects in relation with radiographic procedures, which include the use of non-ionic monomeric contrast media. For side effects specific to mode of administration, please refer to these specific sections.

Serious reactions as well as fatalities are only seen on very rare occasions.

Hypersensitivity reactions usually present as respiratory or cutaneous symptoms like dyspnoe, rash, erythema, urticaria, pruritus, skin disorder, angioneurotic oedema, laryngeal oedema, bronchospasm or pulmonary oedema. They may appear either immediately after the injection or up to a few days later.

Hypersensitivity reactions may occur irrespectively of the dose and mode of administration and mild symptoms may represent the first signs of a serious anaphylactoid reaction/shock. Administration of the contrast medium must be discontinued immediately and, if necessary,

specific therapy instituted via the vascular access. Patients using beta-blockers may present with atypical symptoms of anaphylaxis, which may be misinterpreted as a vagal reaction.

An undesirable effect is said to be:

- very frequent if its frequency is ≥ 10%
- common if its frequency is between ≥ 1% and < 10%
- uncommon if its frequency is between ≥ 0.1% and < 1%
- rare if its frequency is between ≥ 0.01% and < 0.1%
- very rare if its frequency is < 0.01%

Reactions, for which no frequency rate can be provided due to lack of clinical data, have been entered with 'Not known'.

The listed frequencies are based on internal clinical documentation and published large-scale studies, comprising more than 200,000 patients.

MedDRA System Organ Class	**Adverse Drug Reaction (ADR)**	**Frequency**
Immune system disorders	Hypersensitivity (may be life-threatening or fatal) Anaphylactic/Anaphylactoid reaction (may be life-threatening or fatal) Anaphylactic/Anaphylactoid shock (may be life-threatening or fatal)	Rare Very rare Not known
Nervous system disorders	Headache Dysgeusia Syncope vasovagal	Uncommon Very rare Very rare
Cardiac disorders	Bradycardia	Rare
Vascular disorders	Hypertension Hypotension	Very rare Very rare
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Abdominal pain/discomfort Salivary gland enlargement	Uncommon Rare Very rare Rare Not known
General disorders	Feeling hot Pyrexia Chills Hyperhidrosis	Common Rare Very rare Very rare
Injury, poisoning and procedural complications	Iodism	Not known
Endocrine disorders:	Hypothyroidism*	Uncommon

*Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism

Intravascular Use (Intra-arterial and Intravenous Use)
Please first read the section labelled "General". Below, only undesirable events with frequency during intravascular use of OMNIPAQUE are described.

The nature of the undesirable effects specifically seen during intraarterial use depends on the site of injection and dose given. Selective arteriographies and other procedures in which the contrast medium reaches a particular organ in high concentrations may be accompanied by complications in that particular organ.

A transient increase in S-creatinine is common after iodinated contrast media, but usually is of no clinical relevance.

MedDRA System Organ Class	**ADRs**	**Frequency**
Endocrine disorders	Thyrotoxicosis Transient hypothyroidism	Not known Not known
Psychiatric disorders	Confusional state Anxiety Agitation	Not known Not known Not known
Nervous system disorders	Convulsion Motor dysfunction Sensory disturbance (including dysgeusia, hypoesthesia paraesthesia) Transient contrast induced encephalopathy (including amnesia, hallucination, paralysis, paresis, disorientation, transient speech disorder, aphasia, dysarthria) Disturbance in consciousness Tremor Dizziness	Very rare Not known Very rare Not known Very rare Very rare Rare
Eye disorders	Blindness transient Transient visual impairment (including diplopia, blurred vision	Not known Not known
Ear disorders	Transient hearing loss	Not known
Cardiac disorders	Arrhythmia Cardiac arrest Myocardial ischaemia Ventricular hypokinesia Spasm of coronary arteries Myocardial infarction Chest pain	Rare Not known Not known Not known Not known Very rare Very rare
Vascular disorders	Flushing Arterial spasm Ischaemia Thrombophlebitis Thrombosis Shock Hypertension	Very rare Not known Not known Not known Not known Not known Very rare
Respiratory, thoracic and mediastinal disorders	Cough Dyspnoea Non-cardiogenic pulmonary oedema Bronchospasm	Very rare Very rare Very rare Not known

	Laryngospasm Asthma attack	Not known Not known
Gastrointestinal disorders	Pancreatitis aggravated	Not known
Skin and subcutaneous tissue disorders	Bullous dermatitis Stevens-Johnson syndrome Erythema multiforme Toxic epidermal necrolysis Acute generalised exanthematous pustulosis Drug rash with eosinophilia and systemic symptoms Psoriasis flare-up Rash Pruritus Urticaria Angioedema	Not known Not known Not known Not known Not known Not known Not known Rare Rare Rare Not known
Musculoskeletal, connective tissue and bone disorders	Arthralgia Back pain	Not known Not known
Renal and urinary disorders	Acute kidney injury Blood creatine increase	Uncommon Not known
General disorders	Feeling hot Pain and discomfort Injection site reaction Asthenic conditions (eg. Malaise, fatigue) Extravasation	Common Uncommon Not known Very rare Not known

Intrathecal use
Please first read the section labelled "General". Below, <u>only</u> undesirable events with frequency during intrathecal use of non-ionic monomer contrast media are described.

Undesirable effects following intrathecal use may be delayed and present some hours or even days after the procedure. The frequency is similar to lumbar puncture alone.

MedDRA System Organ Class	**ADR**	**Frequency**
Psychiatric disorders	Confusional state Anxiety Agitation	Not known Not known Not known
Nervous system disorders	Headache Meningitis chemical Convulsion Dizziness Electroencephalogram abnormal Meningism Motor dysfunction Paraesthesia Sensory disturbance Seizures Transient contrast-induced (including amnesia, hallucination, paralysis,	Very frequent Uncommon Rare Rare Not known Not known Not known Not known Not known Not known Not known

	paresis, disorientation, transient speech disorder, aphasia, dysarthria) Dysgeusia	 Not known
Eye disorders	Visual impairment (including diplopia and blurred vision) Blindness transient Photophobia	Rare Not known Not known
Ear disorders	Transient hearing loss	Not Known
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	Common Common Rare
Musculoskeletal, connective tissue and bone disorders	Pain in extremity Neck pain Muscle spasms Back pain	Rare Rare Not known Not known
General disorders	Injection site reaction	Not known

Headache, (which may be severe and lasting), nausea, vomiting or dizziness may largely be attributed to pressure loss in the subarachnoid space resulting from leakage at the puncture site. Excessive removal of cerebrospinal fluid should be avoided in order to minimise pressure loss.

Use in Body Cavities
Please first read the section labelled "General". Below, only undesirable events with frequency during use of non-ionic monomeric contrast media in body cavities are described.

Endoscopic Retrograde Cholangiopancreatography (ERCP):

MedDRA System Organ Class	**ADRs**	**Frequency**
Gastrointestinal disorders	Pancreatitis Blood amylase increased	Common Common

Oral use:

MedDRA System Organ Class	**ADRs**	**Frequency**
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Very frequent Common Common Uncommon

Hysterosalpingography (HSG):

MedDRA System Organ Class	**ADRs**	**Frequency**
Gastrointestinal disorders	Abdominal pain	Very frequent

Arthrography:

MedDRA System Organ Class	**ADRs**	**Frequency**
Musculoskeletal, connective tissue and bone disorders	Arthritis	Not known
General disorders	Pain	Very frequent

Herniography:

MedDRA System Organ Class	**ADRs**	**Frequency**

General disorders	Pain	Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Preclinical data indicate a high safety margin for OMNIPAQUE and no fixed upper dose level has been established for routine intravascular use. Symptomatic overdosing is unlikely in patients with normal renal function unless the patient has received an excess of 2000 mg I/kg body-weight over a limited period of time.

The duration of the procedure is important for the renal tolerability of high doses of contrast media ($t_{½}$ ~ 2 hours). Accidental overdosing is most likely following complex angiographic procedures in children, particularly when multiple injections of contrast medium with high-concentration are given.

Clinical consequences of overdosage with OMNIPAQUE have not been reported. However, based on experience with other non-ionic myelographic media, physicians should be alert to a potential increase in the frequency and severity of CNS-mediated reactions. Even use of the 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 maximum recommended dose of OMNIPAQUE by intrathecal administration is 3 g of iodine.

In cases of overdose, any resulting water or electrolyte imbalance must be corrected. Renal function should be monitored for the next 3 days. If needed, haemodialysis may be used for clearance of excessive contrast medium. There is no specific antidote.

In case of overdose, immediately contact the Poisons Information Centre for advice, in New Zealand, call 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: X-ray contrast media, iodinated. ATC code: V08AB09

Intravascular Use

For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iohexol in healthy volunteers, no significant deviation from preinjection values has been found. The few changes observed in the laboratory parameters were minor and considered to be of no clinical importance.

A study was performed in 129 patients with diabetes and impaired renal function (serum creatinine levels from 115-308 µmol per litre) to compare a low osmolar (LOCM) and an isosmolar contrast medium (IOCM). Iohexol, as a representative of LOCM was compared to an IOCM in this high-risk population. The results showed 26% of the patients experiencing a rise in

serum creatinine of > 44.2 µmol per litre and 15% of patients with a rise of >88.4 µmol per litre, which is in line with expected incidence of CIN.

Iohexol provides opacification of blood vessels and permits radiographic visualisation until sufficient haemodilution occurs or sufficient contrast medium has left the site of injection.

Being a non-ionic compound, iohexol yields solutions of lower osmolality than the conventional ionic contrast media. Intravenous or intra-arterial injection of iohexol causes less pain and sensation of heat than conventional ionic media with similar iodine content. Iohexol solutions cause less cardiac and vascular disturbances on intravascular injection. The transit time of iohexol through the coronary vascular system is slightly increased compared with conventional ionic contrast media, probably due to the increased viscosity of iohexol at comparable iodine concentrations.

The period of maximal opacification of the renal vessels may begin as early as 30 seconds after i.v. 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.

Intrathecal Use
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 diagnostic contrast that can be achieved.

Following subarachnoid injection, OMNIPAQUE will continue to provide good diagnostic contrast by conventional radiography for at least 30 minutes. Slow diffusion of iohexol takes place throughout the CSF as well as transfer into the circulation. At approximately 1 hour, contrast of diagnostic quality will not usually be available for conventional myelography. However, sufficient contrast for CT myelography will be available for several hours. If CT myelography is to follow, it should be deferred for several hours to allow the degree of contrast to decrease.

Following lumbar subarachnoid placement, irrespective of the position in which the patient is later maintained, slow upward diffusion of OMNIPAQUE takes place throughout the CSF. CSF contrast enhancement for CT scanning may be expected 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 after administration into the lumbar subarachnoid space.

Clinical Trials
Body Cavities and Oral Use:
A number of clinical trials have been carried out administering OMNIPAQUE into various body cavities including the oral route. There have been six studies using diluted OMNIPAQUE orally through a feeding tube or rectally in infants and children as a contrast agent in the gastrointestinal tract with good results. This procedure is advantageous when barium sulphate is contraindicated. Excellent images are obtained. In double-contrast arthrography, a randomised-double blind study (n=132) in patients with shoulder pain showed that image quality was good or excellent on CT examination in 96.1% of the group. Five studies have been carried out showing success in hysterosalpingography. There are four clinical studies using OMNIPAQUE in endoscopic retrograde cholangiopancreatography (ERCP). It was found that

LOWS (low osmolality water soluble) media (OMNIPAQUE) reduce the frequency and severity of post-procedural pancreatitis compared with higher osmolality ionic contrast agents.

Efficacy for contrast agents is usually judged pragmatically by the adequacy of diagnostic information obtained. The primary outcome is the overall quality of visualisation and the secondary outcome includes good contrast opacity and satisfactory mucosal coating.

5.2 Pharmacokinetic properties

Intravascular Use

87-99 per cent of the intravenously injected iohexol is excreted unchanged through the kidneys within 24 hours in patients with normal renal function. The maximum urinary concentration of iohexol appears within approximately 1 hour after injection. The elimination half-life is approximately 2 hours in patients with normal renal function. No metabolites have been detected. The protein binding of OMNIPAQUE is so low (less than 2 %), that it has no clinical relevance and can therefore be neglected.

Intrathecal Use

Following injection into the lumbar subarachnoid space, iohexol is absorbed from CSF into the bloodstream and is eliminated by renal excretion.

After lumbar administration of 10-15 ml iohexol at a concentration of 180 mg I/ml to 6 patients, a mean maximum concentration of 0.024 mg I/ml was observed after a mean of 2.2 hours. The mean half-life of the initial rapid distribution phase from blood was 34 minutes and for the slower elimination phase was 3.4 hours.

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 described previously. Examinations of the uterus (hysterosalpingography) involve the most immediate drainage of contrast medium from the cavity upon conclusion of the radiographic procedure. Iohexol is well tolerated and readily absorbed if leakage into the peritoneal cavity occurs.

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

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

5.3 Preclinical safety data

Iohexol has a very low acute intravenous toxicity in mice and rats. Animal studies have shown that iohexol has a very low protein binding and is well tolerated by the kidneys. The cardiovascular and neurotoxicity are low. The histamine release ability and the anticoagulant activity have been shown to be less than for ionic contrast media.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each millilitre of iohexol solution also contains 1.2 mg of tromethamine USP and 0.l mg of edetate calcium disodium USP with the pH adjusted between 6.8 and 7.6 with hydrochloric acid or sodium hydroxide. Solutions are sterilised by autoclaving and contain no preservatives.

6.2 Incompatibilities

Although no incompatibility has been found, OMNIPAQUE should not be directly mixed with other drugs. A separate syringe should be used.

6.3 Shelf life

Glass or polypropylene bottles (10 – 150 ml): 36 months.
Polypropylene bottles (200 – 500 ml): 24 months.

6.4 Special precautions for storage

OMNIPAQUE should be stored at 2-30ºC protected from light and secondary X-rays. The product in glass vials and bottles may be stored at 37ºC for up to 3 months prior to use.

The product in 50 ml polypropylene bottles may be stored at 37ºC for up to 1 month prior to use. The product in 10 ml and 20 ml polypropylene bottles may be stored at 37ºC for up to 1 week prior to use.

6.5 Nature and contents of container

240 mg I/ml	20 ml	Packs of 6 or 25 glass bottles and 10 polypropylene bottles
	50 ml	Packs of 10 glass or polypropylene bottles
	500 ml	Packs of 6 bottles
300 mg I/ml	10 ml	Packs of 10 glass or polypropylene bottles
	20 ml	Packs of 6 or 25 glass bottles and 10 polypropylene bottles
	50 ml	Packs of 10 glass or polypropylene bottles
	75 ml	Packs of 10 glass or polypropylene bottles
	100 ml	Packs of 10 glass or polypropylene bottles
	150 ml	Packs of 10 polypropylene bottles
	200 ml	Packs of 10 polypropylene bottles
	500 ml	Packs of 6 glass or polypropylene bottles
350 mg I/ml	20 ml	Packs of 6 or 25 glass bottles and 10 polypropylene bottles
	50 ml	Packs of 10 glass or polypropylene bottles
	75 ml	Packs of 10 glass or polypropylene bottles
	100 ml	Packs of 10 glass or polypropylene bottles
	150 ml	Packs of 10 polypropylene bottles
	200 ml	Packs of 6 glass or 6 and 10 polypropylene bottles Packs of
	500 ml	6 glass or 6 and 10 polypropylene bottles

Not all presentations are marketed

6.6 Special precautions for use or disposal

Instructions for Use/Handling

Like all parenteral products, OMNIPAQUE should be inspected visually for particulate matter, discoloration and the integrity of the container prior to use. The product should be drawn into the

syringe immediately before use. Vials are intended for single use only, any unused portions must be discarded.

The 500 ml contrast medium bottles should only be used in connection with auto injectors/pumps approved for this volume. A single piercing procedure should be used.

The line running from the auto injector/pump to the patient must be exchanged after each patient. Any unused portions of the contrast medium remaining in the bottle and all connecting tubes must be discarded at the end of the day. When convenient, smaller bottles can also be used. Instructions from the manufacturer of the auto injector/pump must be followed.

7 MEDICINE SCHEDULE

General Sale Medicine.

8 SPONSOR

GE Healthcare
300 Great South Road
PO Box 17122
Greenlane
Auckland 1130.
Ph (09) 523-5896
Fax (09) 522-7342

9 DATE OF FIRST APPROVAL

8 August 1985

10 DATE OF REVISION OF THE TEXT

3 November 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Additional safety information for beta-adrenergic blocking agents and bronchospasm Additional safety information on kidney injury, paediatric use and encephalopathy.
4.8	Additional adverse events: Back pain Transient hearing loss Visual impairment (including diplopia and blurred vision) Rash Pruritus Urticaria Chest pain