Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Iodixanol

Proprietary Product Name: Visipaque

Sponsor: GE Healthcare Australia Pty Ltd

July 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of indications
Decision:	Approved
Date of Decision:	14 May 2010
Active ingredient(s):	Iodixanol
Product Name(s):	Visipaque
Sponsor's Name and Address:	GE Healthcare Pty Ltd Bld 4B, 21 South Street Rydalmere NSW 2116
Dose form(s):	Solution for Injection.
Strength(s):	270 mg I/ml and 320 mg I/ml (550mg/mL and 652mg/mL)
Container(s):	Colourless highly resistant borosilicate type I glass injection vials (20 mL) and infusion bottles (50, 75, 100, 200 and 500 mL). All closed with chlorobutyl rubber stoppers and sealed with complete tear off caps with coloured plastic "flip-off" tops. Rigid stand-up polypropylene (PPE) bottles of 10, 20, 40 and 50 mL with a twist-off top. Polypropylene bottles of 50, 75, 100, 150, 175, 200 and 500 mL closed with chlorobutyl rubber stoppers and supplied with a plastic screw cap which is provided with a tamper proof ring.
Pack size(s):	20, 50, 100, 150 mL glass vials and 50, 100, 150, 200 mL PPE bottles; boxes of 10 200 ml glass bottles; boxes of 6 10, 20, 40, 50 mL PPE ampoules; boxes of 10 100, 150 and 200 mL bags
Approved Therapeutic use:	This medicinal product is for diagnostic use only. Visipaque is indicated in adult patients for angiocardiography, peripheral arteriography, visceral arteriography, cerebral arteriography, contrast-enhanced computed tomography of the head and body, excretory urography and venography. In arteriography, Visipaque may be used for both conventional radiography and digital subtraction angiography (DSA). In children, Visipaque is indicated for cardioangiography, urography, CT enhancement and studies of the upper gastrointestinal tract.
Route(s) of administration:	Intravascular injection
Dosage:	Varies with the diagnostic procedure and the state of the patient
ARTG Numbers:	49594, 49597, 49598, 49599, 49600, 49601, 49602, 49603, 49604, 49605, 49606, 49607, 49608, 49609, 75923, 75924,

75925, 75926, 75927, 75928, 75929, 75930, 154369, 154369

Product Background

This is an application to extend the indications of Visipaque (iodixanol) to include paediatric use. In children the proposed indications are:

Visipaque is indicated for cardioangiography, urography, CT-enhancement and studies of the upper gastrointestinal tract.

Iodixanol, is a non-ionic, water-soluble and hexa-iodinated dimer which has a lower osmolality than whole blood. Visipaque was approved for use in adults in Australia in 1995. Visipaque is currently indicated, in adult patients, for angiocardiography, visceral arteriography, cerebral arteriography, contrast-enhanced computer tomography of the head and body, excretory urography and venography. The product is for diagnostic use only.

Regulatory Status

The product received initial ARTG Registration in 1995.

Marketing authorisations for Visipaque have been granted in a total of 86 countries worldwide, both for intra-arterial and intravenous administration. The product is also approved for paediatric use in 71 countries including the European Union (EU), the USA, New Zealand and Switzerland.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared is at Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There is no requirement for a quality evaluation in an application of this type.

III. Nonclinical Findings

Introduction

The sponsor has applied for approval for use in paediatric patients of all ages (no age limit in the proposed product information [PI]) by the intra-arterial (IA), intravenous (IV) and oral (PO) routes. Two strengths of the product are available (270 and 320 mg I/mL). The paediatric doses depend on age, weight and pathology (Table 1).

Table 1: Proposed paediatric doses

Route, indication	Concentration (mg I/mL)	Volume
IA, cardioangiography	320	Depending on age, weight and pathology (max. 10 mL/kg)
IV, urography (< 7 kg)	270, 320	2-4 mL/kg
(> 7 kg)	270, 320	2-3 mL/kg
		All doses depend on age, weight and pathology (max. 50 mL)
CT-enhancement	270, 320	2-3 mL/kg up to 50 mL
PO, gastrointestinal studies	320	5 mL/kg (10-240 mL has been studied) The dosage must be adjusted individually to allow optimal visualisation.

No new nonclinical studies were provided in the submission. The sponsor provided reports of reproductive toxicity studies and a juvenile study, which had been previously evaluated by TGA for the initial new chemical entity application, and an overview and summaries of these studies. The sponsor's justifications for not providing new nonclinical studies were:

1) toxicity after a single administration in juvenile and adult rats was similar;

2) safety data from adult exposure would usually represent the most relevant information according to the International Conference on Harmonization (ICH) M3 guideline adopted by the European Medicines Agency (*CPMP/ICH/286/95: Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*); and

3) safety and efficacy of Visipaque have been established in the paediatric population for arterial and intravenous procedures.

According to the sponsor, the paediatric use has been approved in many countries including the UK, Sweden, the Netherlands, New Zealand and the USA (*Section I*).

The nonclinical studies relevant to the paediatric indication are the rat juvenile study and peri-/postnatal study. Since the previous evaluation report documented only clinical signs and the median lethal dose (LD_{50}) value for the juvenile study, more information on the juvenile study is included below. The peri-postnatal study is briefly summarised on the basis of the previous evaluation report.

Toxicology

In the juvenile rat study, iodixanol (320 mg I/mL) was administered IV in a tail vein to male and female rats of 19-21 days old at 17.5 or 21.0 g I/kg at a rate of 1.2 mL/min. At the low dose (LD), 5 out of 14 females and 6 out of 15 males died, and 7 out of 11 males and 7 out of 13 females died at the high dose (HD). Mortalities occurred within 10 minutes of dosing with the exception of two rats (dose group not reported), which died 17 and 32 minutes after dosing. The LD_{50} was 19-20 g I/kg. Clinical signs of the pups that died were inability to move and respiratory difficulties immediately after dosing. Surviving rats exhibited heavy breathing and sedation. Most survivors recovered within 2 hours of dosing. Necropsy of the dead animals showed pulmonary oedema and haemorrhage. There were no gross findings in survivors 7 or 14 days after dosing, but proximal tubule vacuolation of the kidney (the only organ microscopically examined) was observed.

The LD_{50} in juvenile rats was lower than in adult rats (LD_{50} > 21 g I/kg). The study author suggested that the higher death rates in young rats were probably due to the faster speed of injection (1.2 mL/min in 35-48 g pups, that is, 0.025-0.034 mL/min/g) compared to the study in adult rats (2.0 mL/min in 100-150 g rats, that is, 0.013-0.02 mL/min/g). It was also possible that deaths in the young rats were due to immature renal functions in juveniles.

In the peri/post-natal study in rats, dams were dosed with 0.3, 1 or 2 g I/kg iodixanol from gestation day 17 to day 21 post-partum. The only effects were slightly lower body weights of F1 and F2 pups at weaning (by 2.5% and about 5%, respectively, compared with the control group) at the HD and lower body weights of F1 rats post-weaning at the MD (mid-dose) and HD (about 5%), with statistical significance attained at the HD. Pup exposure to iodixanol was not determined in the study.

Nonclinical Summary and Conclusions

Previously evaluated data showed that iodixanol is mainly eliminated by renal excretion. The main target organ of toxicity is the kidney, which displayed increased organ weight and cortical tubular epithelial vacuolation and basophilia. Arterial hypotension was seen in rats, but not in rabbits or dogs.

The single dose toxicity study in juvenile rats dosed with iodixanol IV indicated that iodixanol was more toxic in immature animals than in adults probably as a result of immature renal functions in juveniles and/or the faster injection speed in the juvenile rat study compared to the study in adult rats. As indicated by the sponsor, clinical signs in juvenile rats were similar to those observed in adult rats. There were no repeat dose toxicity studies in juvenile animals. While in most cases patients receive a single dose of iodixanol, the ICH guideline M3 recommends repeat dose studies for up to 2 weeks for single dose pharmaceutical products. The peri-/postnatal study showed only minor findings (decreased body weights) in rat pups, but the study is of little value for the assessment of the safety in children since there was no pup exposure data.

Iodixanol is proposed to be used in paediatric patients by the IV, IA and oral routes. While the IV and IA routes have been approved for use in adults, the oral route is not an approved route of administration in adults in Australia. There are no nonclinical data on absorption and toxicity by the oral route.

The available nonclinical juvenile data are insufficient to support the paediatric use of iodixanol. The single dose study in juvenile rats indicates that iodixanol is more toxic in juveniles than in adults. The main concerns for paediatric use are the potential renal toxicity in very young children with immature renal functions and potential cardiovascular effects due to higher exposure as a result of slower elimination of iodixanol in children than in adults. In addition, there are no nonclinical toxicity studies by the oral route. Thus, potential adverse effects in paediatric patients by the oral route are unknown.

As indicated in the ICH guideline M3, safety data from adult exposure usually represent the most relevant information for paediatric use. For this application, safety data in renally impaired adults is of particular importance in the assessment of safety in young children with immature renal functions. If the application is approved on the basis of adequate clinical safety data, changes to the PI are recommended.

IV. Clinical Findings

Introduction

Following discussion held with the TGA a hybrid submission containing some original clinical research studies together with an updated literature search was submitted.

The studies submitted for evaluation included:

- Study Report 2493: A Phase I open-label, multicentre, pharmacokinetic and safety trial in paediatric patients, newborn to 12 years of age.

The following ten paediatric clinical studies were Phase III, double-blind, parallel group randomised and controlled trials comparing safety and efficacy of Visipaque with iohexol

Excretory Urography

- Study DXV041
- Study DXV037

*Cranial Computed Tomograph*y

- Study DXV039

· Study Report 1966

Computed Tomography of Body
· Trial DXV038
· Study Report 1967

Angiocardiography Studies
· Study DXV036
· Study Report 1968

Gastrointestinal Studies
· Study DXC060
· Study DXC064

Pharmacodynamics

There were no pharmacodynamics data submitted.

Pharmacokinetics

Study Report 2493

This was a Phase I open-label, multicentre, pharmacokinetic and safety trial in paediatric patients, newborn to 12 years of age who were referred for contrast-enhanced radiographic procedures between 12 April 1995 to 18 December 1995. The trial was conducted in compliance with the US Code of Federal Regulations governing informed consent, Institutional Review Boards and with applicable regulations governing sponsor/monitor conduct. A routine clinical audit of the study was conducted by the sponsor's Quality Assurance Department.

Objectives

1. To determine the pharmacokinetic profile of iodixanol injection 320 mg I/mL (VIS-320) in plasma. The primary PK endpoint was the terminal elimination rate constant (k_{el}).
2. To assess the safety of VIS-320 by evaluating adverse events, injection-associated discomfort/distress, vital signs and clinical laboratory parameters, and in angiocardiography patients only, haemodynamics and electrocardiograms (ECGs).

Pharmacokinetics

The concentration versus time curve was estimated by a one-compartment model with first order elimination. The terminal elimination rate constant (k_{el}) was computed by linear regression of the natural logarithm of the plasma concentration as a function of time. The half life ($t_{½}$) was calculated as = 0.693 k_{el}).

Safety

Adverse events (AEs) were evaluated during the procedure and for at least one hour after the last injection. Patients were followed for between 16 to 32 hours and re-assessed three days after the procedure.

Injection associated discomfort was evaluated during VIS-320 injection and within one minute post-injection either by the patient's assessment or by observation of behavioural response.

Haematology and blood chemistry parameters and where possible, urinalysis, were evaluated within 24 hours before administration and between 16 and 32 hours after the procedure.

Blood pressure and pulse rate were measured immediately before the procedure and immediately after the conclusion of the procedure and between 16 to 32 hours after the procedure. For patients undergoing angiocardiography, blood pressure was monitored during the procedure and Lead-II ECG monitoring was traced continuously during the procedure.

Efficacy

Evaluation of efficacy was not an endpoint; however, the quality of enhancement for the radiographic procedure was evaluated and was rated by the investigator as:

Inadequate	Insufficient quality of enhancement or visualisation to make a diagnosis
Poor	Marginal contrast enhancement or visualisation but adequate to make a diagnosis
Good	Sufficient contrast enhancement or visualisation
Excellent	Superior contrast enhancement of visualisation

Patient Enrolment and Demographic Characteristics

A total of 43 patients were enrolled into five groups shown below. All patients completed the trial.

Newborn to < 2 months	8 patients
2 to < 6 months	9 patients
6 to < 12 months	10 patients
1 year to < 3 years	8 patients
3 to 12 years	8 patients

Participants included 27 males and 16 females. The majority were Caucasian (60%) or Black (35%). The mean age was 1.87 years, range < 1 day to 10.41 years. The mean weight was 9.7 kg; range 3 to 40 kg; Mean height was 75.8 cm; range 48 to 150 cm.

The most common referring diagnoses were ventricular septal defect (17 patients), patent ductus arteriosus (8), aortic stenosis (7), tetralogy of Fallot, atrial septal defect and pulmonary atrial/ventricular stenosis (6 each) and aortic hypoplasia (5). At enrolment there were 9 patients with congestive heart failure, 6 with ventricular septal defect and Down syndrome and 5 patients with heart murmurs. Eight patients had undergone surgery for their medical conditions prior to enrolment. Twenty-four patients had more than one referring diagnosis.

Inclusion Criteria

- Patients from 36 weeks gestation age to 12 years inclusive referred for iodinated, contrast –enhanced intravascular diagnostic procedures including, but not limited to angiocardiography, computerised tomography (CT) scanning of the head and CT scanning of the body.
- ≥ 2000 g body weight
- Signed, witnessed and informed consent
- Willing to be available for follow-up observations
- Negative pregnancy screen for females of childbearing potential

Exclusion Criteria

- Patients who had received or were scheduled to receive an unapproved investigational drug within 30 days before or 24 hours after the trial
- Patients examined with or scheduled to receive an iodinated contrast agent within 72 hours before or 24 hours after the trial
- For a patient less than 3 days old, receipt by patient's mother of an iodinated contrast agent within 48 hours before giving birth

- Patients who required an iodinated oral contrast agent for the procedure
- Patients with known or suspected serious reaction to iodinated contrast agents
- Patients previously entered into this trial
- Patients who were scheduled for surgery or general anaesthesia during the 16 – 32 hour follow-up period
- Patients who were scheduled for interventional procedures other than biopsy, balloon atrial septostomy, embolisation that did not require an investigational device, balloon dilatation of aortic or pulmonary valves, or snare closure of atrial septal defects during the radiographic procedure or the one day follow-up period in accordance with Protocol Amendment A-03. The original protocol permitted the following: biopsy, balloon atrial septostomy or coil embolisation.
- Patients in a clinically unstable condition
- Patients with a serious intercurrent illness
- Patients with a known or suspected intracranial haemorrhage within 6 months
- Patients with known or suspected abnormal renal function

Study Treatment

All patients received VIS-320 by intra-arterial or intravenous injection and dosing was performed according to each trial centre's standard procedures. Drug information for iohexol injection 350 mg I/mL was provided as a guide to the investigators: up to 5.0 mL/kg for intra-arterial administration and 3.0 mL/kg for intravenous administration.

Statistical Methods

The sample size of 40 patients was chosen empirically. Pooled data from the centres was analysed. For safety endpoints, proportions of patients with one or more adverse events were summarised overall and by age group. A logistic regression analysis was performed with the indicator of presence of one or more adverse events as the dependent variable and age as a continuous independent variable. Categorical safety endpoints were summarised.

Clinical laboratory samples from patients were processed at different laboratories with different reference ranges. Laboratory values were compared with their respective reference ranges. Changes from baseline were calculated from observed values, not from values standardised to the reference range. Observed values and changes from baseline were summarised. 95% confidence intervals (CI) were provided for the mean changes from baseline.

Pharmacokinetic Results

Forty-three patients were enrolled. Two patients underwent computed tomography and were administered VIS-320 intravenously. All other patients underwent angiocardiography and were administered VIS-320 intra-arterially.

Two patients with incomplete PK sampling data were excluded from analyses of PK data and were replaced in this trial. The one patient who developed renal failure and who died was also excluded from the PK analyses. One patient was entered into the trial in error as the ninth patient in the 6 month to < 1 year age group. Results for this patient were included in the analyses. Drug administration is summarised in Table 2.

Table 1: Study Report 2493

Distribution of Angiocardiography Procedural Injections

Injection Site	Number of Patients With ≥1 Injections	Total Number of Injections
Any	41	112
Aorta	24	33
Left ventricle	22	27
Right ventricle	18	21
Other*	13	20
Pulmonary arteries	5	11

*Includes the following injection sites: superior vena cava, right atrium, femoral venous system, right internal mammary artery, right external thoracic, lumbar 1-2, left atrium, truncus, left scapuloanterior, innominate artery, and left pulmonary ventricular wedge.

The mean dose was 1.49 g I/kg. The mean total volume was 4.67 mL/kg. The mean number of procedural injections per patient was 2.7. The mean doses for patients≥ 3 years of age were approximately half that for patients < 3 years of age. The mean duration of the procedure from beginning of the first injection to the end of the last injection was 30 minutes.

The mean k_{el} results were:

Newborn to < 2 month	0.185/hr
2 to < 6 month	0.256/hr
> 6 months	0.299 – 0.322/hr

The mean k_{el} was significantly lower in the newborn to < 2 months age group than in any of the three oldest age groups; $p \leq 1.0001$ for each comparison with no adjustment for multiplicity. The 2 to < 6 month age group mean k_{el} was intermediate between the youngest and older patients (Table 3).

Table 2: Study Report 2493

Mean Observed Terminal Elimination Rate Constants (k_{el}), as a Percentage of Adult Elimination Rate Constants, by Age Group[a]

Age Group	Observed k_{el}
Newborn to <2 months	55%
2 to <6 months	76%
6 months to <1 year	89%
1 to <3 years	96%
3 to ≤12 years	91%

[a] Expressed as a percentage of the adult elimination rate constant (k_{el}), from the Phase I study in normal male adult volunteers (0.336 hr^{-1}).

Modelling with segmented linear regression found increasing k_{el} from birth to approximately 0.55 years (95% CI 0.36 – 0.75 years). This model was used to calculated $t_{½}$. In infants < 2 years of age, the $t_{½}$ of iodixanol was approximately 4.1 hours. For children 2 – 6 months of age the $t_{½}$ was approximately 2.8 hours. In children > 6 months of age but < 12 years, the $t_{½}$ was 2.3 hours, approximating that of adult with normal renal function of 2.1 hours. (Table 4)

Table 3: Study Report 2493

Summary Statistics for Terminal Elimination Rate Constant (k_{el}) and Half-Life ($t_{½}$) by Age Group

Age Group	k_{el} (hr^{-1})			$t_{½}$ (hr)	
	N	Mean	SD	Mean	SD
Newborn to <2 months	8	0.185	0.060	4.14	1.41
2 to <6 months	8	0.256	0.046	2.79	0.55
6 months to <1 year	9	0.299	0.042	2.36	0.37
1 to <3 years	7	0.322	0.058	2.23	0.51
3 to ≤12 years	8	0.307	0.071	2.36	0.52

Efficacy

Study Report 2493 - Efficacy Results

All 43 patients enrolled and dosed completed the study and were included in the efficacy analyses. The quality of visualisation or enhancement was considered adequate for diagnosis in all 43 patients and was considered excellent for 41 (95%) and good for 2 (5%)

Characteristics Common to Efficacy and Safety Studies

The same basic trial protocol with some local differences applied to the studies of excretory urography, cranial computed tomography and computed tomography of the body. These six trials were Phase III, double-blind, parallel group paediatric studies of safety and efficacy of iodixanol 320 mg (VIS-320) and iodixanol 270 mg I/mL (VIS–270) compared to iohexol 300 mg I/mL. In each study 75 patients were planned for enrolment to be randomly allocated to three groups of 25 patients. Two angiocardiography studies with similar design were included in which patients were assigned to receive either VIS-320 or iohexol 350 mg I/mL.

Randomisation was computerised. The trial drugs were either delivered in vials of identical appearance or were dispensing by personnel not associated with the patient assessments.

Although the studies were designed to consist of two parts, the first being an open Phase II pilot study, only Studies DXV0141 and DXV036 actually included this component. The results for these two pilot studies were not incorporated into the main body of the reports.

In addition two gastrointestinal contrast studies were included in which patients were assigned to receive test agent Visipaque 150 mg I/mL, 320 mg I/mL or 270 mg I/mL or comparator Omnipaque (iohexol) 140 mg I/mL or 300 mg I/mL.

Efficacy Evaluation

Efficacy was assessed by investigator evaluation and scoring of

· The overall diagnostic information

- The ability to obtain a radiographic diagnosis
- The diagnostic utility of the contrast medium

In most instances, two investigators evaluated efficacy for all patients and reached a consensus. Diagnostic information was evaluated for the parenchyma, calyces, pelvis and ureter. The quality of visualisation was graded as follows:

Excellent	Superior contrast visualisation
Good	Sufficient contrast visualisation
Poor	Marginal contrast visualisation but adequate to make a diagnosis
Inadequate	Insufficient visualisation to make a diagnosis

In those cases rated as poor or inadequate, an explanation was to be given

The referring and radiographic diagnoses were coded according to the Fourth Edition of the American College of Radiology's Index of Radiological Diagnosis, 1992. Assessment of the diagnostic utility of the contrast medium in relation to the referring diagnosis and/or presenting symptoms was evaluated by questioning whether the contrast-enhanced images confirmed, ruled out or failed to allow comparison with the referring diagnosis and/or presenting symptoms. The image quality of the most recently performed (non-trial) urography examination was compared to the post-injection examination in this trial.

Inclusion Criteria

- Inpatients or outpatients of either sex, referred for the relevant contrast-enhanced study
- Age 0 to up to the age limit specified for individual studies, maximum 18 years
- Signed, written informed consent obtained from the parent(s)/guardians(s) and where possible assent from the child.

Exclusion Criteria

- Previous inclusion in this study
- Clinically unstable condition
- Pregnant or breast feeding
- Previous serious reactions to iodine-containing contrast media
- Intravascular iodinated contrast medium injection within 1 week prior to this examination for patients younger than 2 years, or within 48 hours for patients older than 2 years
- Scheduled to receive and iodinated contrast medium intravascularly within 24 hours after the examination
- Use or planned use of an unregistered drug during the 30 days prior to, or within 24 hours after the examination
- Scheduled to undergo surgery or general anaesthesia within 24 hours following the examination

Statistical methods

For multicentre studies, data for individual study centres were pooled. The planned statistical analysis in the protocol was not in accordance with the stated objectives of the study which was to compare findings between each of the iodixanol concentration groups versus the iohexol group. The plan was altered to the following:

For the studies including two formulations of iodixanol, two pairwise comparisons of proportions of patients with any adverse events VIS-270 versus iohexol and VIS-320 versus iohexol, using Fisher's Exact tests for 2 x 2 tables. For each of the right and the left kidney

results two pairwise comparisons were preformed for VIS-320 and for VIS-270 versus iohexol using Wilcoxon Rank-sum sample tests.

Study DXV041 – Excretory Urography

The study was conducted in Sweden between March 1994 and February 1995.

Phase II

Three female patients aged between 3 years 8 months and 4 years 7 months were enrolled in the pilot study. Two patients were administered VIS-320 and one was administered VIS-270. The total volumes injected ranged from 30 – 35 mL. The patient who received VIS-270 had a dose of iodine of 0.54 g I/kg. The patients who received VIS-320 each had a dose of 0.64 g I per kg body weight. The overall diagnostic information was judged to be excellent or good.

Phase III

The study was conducted at three centres in France between May 1994 and June 1995. A total of 75 patients were enrolled; 72 patients aged three weeks to 15 years were included in the analyses. Individuals with weight lower than 2500 g at the time of examination, or with any other clinical signs of prematurity were excluded from the study. Patients were stratified according to whether they were below or above 2 years of age.

Exclusion criteria in this study not common to all studies included:

- Weight lower than 2500 g at the time of examination, or any other clinical signs of prematurity
- Suspicion of acute or chronically reduced renal function and serum creatinine measured to be > 200 µmol/L
- Receiving nephrotoxic medication

The dose recommendation was that 3.0 mL/kg should not be exceeded, with a maximum dose of 40 mL. Each patient received only one contrast medium injected through the antecubital vein, hand, foot or scalp vein. The contrast agents were pre-heated to 37°C before injection and injected as a single bolus at a steady slow rate. Local skin anaesthesia (EMLA cream) was used for 80% of patients in each group.

Abdominal compression was performed in accordance with the routine procedure and was used on 16 patients in the VIS-270 group and 17 in each of the other 2 groups. X-rays were taken at 90 sec, 5 and 10 minutes after the injection, after the release of abdominal compression and at the time of maximum filling.

Patient enrolment, characteristics and disposition

75 patients were enrolled and all completed the study.

- VIS-270: 25 patients 15 females and 10 males
- VIS-320 25 patients, 12 females and 13 males
- Iohexol 300 mg I/mL, 25 patients, 14 females and 11 males.

70 patients were Caucasian, 3 were African black and 2 were Oriental. The age ranged from 22 days to 9 years 9 months. Height ranged from 48 to 145 cm and weight ranged from 3 to 36 kg. The main referring diagnoses were pyelonephritis, hydronephrosis and reflux.

Efficacy Results

Protocol deviations: Clinical chemistry, blood and urine parameters planned in the protocol were not done. Abdominal compression routines changed during the conduct of the study and were not required after 27 April 1994

All patients were exposed to the study product. The total volume injected was between 10 and 44 mL. The mean volume of VIS-270 was 30.5 mL corresponding to 8.2 g iodine of 0.53 g I/kg. For VIS-320 the corresponding values were 32.5 mL, 10.4 g iodine or 0.61 g I/kg and for iohexol, 30.1 mL, 9.0 g iodine or 0.61 g I/kg. The maximum amount of iodine per kg body weight was 0.84g in the VIS-270, 1.07g in the VIS-320 and 0.86g in the iohexol group.

Rating of Overall Diagnostic Information (Table 5)

VIS-320 Group

Right kidney: excellent in 22 cases, good in one and poor in two cases

Left kidney: excellent in 32 cases, good in one, poor in 2 cases and in 1 case no rating was given.

VIS-270 Group

For both right and left kidneys the rating was excellent for 19 and good for 6 patients.

Iohexol Group

Right kidney: excellent for 16, good for 8 and poor for 1 case.

Left kidney: excellent for 14 cases, good for 9 and poor for one and in 1 case no rating was given.

Table 4 Study 041 Overall Diagnostic Information

			Iodixanol 270 mgI/ml	Iodixanol 320 mgI/ml	Iohexol 300 mgI/ml
Overall left	DIAGNOSTIC INFORMATION	Excellent	19	21	14
		Good	6	1	9
		Poor	0	2	1
		Inadequate	0	0	0
		Not Applicable	0	1	1
Overall right	DIAGNOSTIC INFORMATION	Excellent	19	22	16
		Good	6	1	8
		Poor	0	2	1
		Inadequate	0	0	0
		Not Applicable	0	0	0

Utility of the Enhancement

In the majority of cases the referring diagnosis was either confirmed or ruled out. For one patient in the VIS-270 group, the contrast enhancement did not allow comparison with the referring diagnosis.

For one patient in the VIS-320, three patients in the VIS-270 and one patient in the iohexol group, another diagnosis was confirmed.

Study DXV037 – Excretory Urography

The study was conducted at three centres in France between May 1994 and June 1995. A total of 75 patients were enrolled; 72 patients aged three weeks to 15 years were included in the analyses. Individuals with weight lower than 2500 g at the time of examination, or with any other clinical signs of prematurity were excluded from the study. As with Study

DXV0141, patients were stratified according to whether they were below or above 2 years of age.

Each patient received only one contrast medium injected which was pre-heated to 37°C before injection and injected as a single bolus at a steady slow rate. The dose recommendation was that 3.0 mL/kg should not be exceeded with a maximum dose of 50 mL.

Patient enrolment, characteristics and disposition

Seventy-five patients were randomised into three groups of 25 patients. Three patients in the VIS-270 did not receive the study product due to prolonged storage in the heating cabinet.

The majority, 68/75, patients were Caucasian, 2 were African black and 1 was Oriental and 1 Other. The age ranged from 3 weeks to 15 years. Height ranged from 52 to 172 cm and weight ranged from 3.6 to 60 kg.

Efficacy Results

The total volume injected was between 6 mL and 50 mL in all groups. The mean volume of VIS-270 was 23.6 mL corresponding to 6.4 g iodine or 0.34 g I/kg. For VIS-320 the corresponding values were 24.4 mL, 7.8 g iodine or 0.56 g I/kg and for iohexol, 27.7 mL, 8.3 g iodine or 0.49 g I/kg. The maximum amount of iodine per kg body weight was 0.56g in the VIS-270, 0.98g in the VIS-320 and 0.71g in the iohexol group.

Rating of Overall Diagnostic Information (Table 6)

VIS-320 Group

Right kidney: excellent in 15 cases, good in 8 and poor in 1 case and inadequate in 1 case. The images rated poor and inadequate were from patients with no right renal secretion.

Left kidney: excellent in 13 cases and good in 12.

VIS-270 Group

Right kidney: excellent for 12 patients, good for 9 patients and poor for 1 patient. None of the images were inadequate.

Left kidney the rating was excellent for 10, good for 8, poor for 2 and inadequate for 2 patients. The inadequate ratings were due to no left renal function in those patients. Images from one patient were rated as poor due to chronic pyelonephritis.

Iohexol Group

Right kidney: excellent for 11 and good for 13

Left kidney: excellent for 8 cases, good for 13, poor for 3 and inadequate for 1 case. Two of the poorly rated cases were due to severe renal obstruction; no reason was obtained for the other poor result. The inadequate result was due to a multicystic dysplastic left kidney.

Table 5 Study 037 Efficacy Results

DRUG	Excellent	Good	Poor	Inadequate
Iodixanol 270 mg I/ml, right/left kidney	12/10	9/8	1/2	0/2
Iodixanol 320 mg I/ml, right/left kidney	15/13	8/12	1/0	1/0
Iohexol 300 mg I/ml, right/left kidney	11/8	13/13	0/3	1/1
Total, right/left kidney	38/31	30/33	2/5	2/3

Utility of the Enhancement

In the majority of cases the referring diagnosis was either confirmed or ruled out. For one patient in the VIS-270 group, the contrast enhancement did not allow comparison with the referring diagnosis.

For two patients in the VIS-320 and one patient in the iohexol group, another diagnosis was confirmed.

Study DXV039 – Cranial Computed Tomography

This study was conducted at a single centre in Sweden between May 1994 and April 1995. Patients were enrolled from birth to 18 years of age and were stratified according to sedation. Exclusion criteria particular to this study included patient weight lower than 2500 g at the time of examination, or any other clinical signs of prematurity; suspicion of acute or chronically reduced renal function and serum creatinine measured to be > 200 µmol/L and patients receiving nephrotoxic medication.

The dose recommended was 3.0 mL/kg with a maximum dose of 150 mL. Each patient received only one contrast medium administered as a single bolus at a steady slow rate of between 0.3 to 0.6 mL/sec. The product was pre-heated to 37° C. Premedication was given according to the hospital routine.

Clinical chemistry, blood and urine parameters planned in the protocol were not done.

Patient enrolment, characteristics and disposition

Seventy five patients were enrolled and all completed the study. The code was not broken for any patient.

- VIS-270: 25 patients 14 females and 11 males
- VIS-320 25 patients, 10 females and 15 males
- Iohexol 300 mg I/mL, 25 patients, 13 females and 12 males

Seventy patients were Caucasian, two were African black and one was Oriental, one was Other and one was not recorded. The age ranged from 5 months to 17 years and 5 months. Height ranged from 65 to 185 cm and weight ranged from 7 to 66 kg.

Efficacy Results

All patients were exposed to one injection of the study product. The total volume injected was between 22 and 150 mL. The mean volume of VIS-270 was 89.1 mL corresponding to 24.1 g iodine of 0.78 g I/kg. For VIS-320 the corresponding values were 89.7 mL, 28.7 g iodine or 0.94 g I/kg and for iohexol, 84.8 mL, 25.4 g iodine or 0.89 g I/kg. The maximum amount of iodine per kg body weight was 0.81g in the VIS-270, 0.96g in the VIS-320 and 0.90 g in the iohexol group.

Rating of Overall Diagnostic Information (Table 7)

The ratings of overall diagnostic information for all formulations were excellent or good except for one in the iohexol group rated inadequate because of motion artefact.

Table 7 Study 039 Efficacy Results – Overall Diagnostic Information

GROUP	Excellent	Good	Poor	Inadequate
Iodixanol 270 mg I/ml	17	8	0	0
Iodixanol 320 mg I/ml	21	4	0	0
Iohexol 300 mg I/ml	18	6	0	1
Total	56	18	0	1

Pre-scans without contrast were done for 19 patients in each iodixanol group and for 22 in the iohexol group. In all cases the contrast enhancement provided additional information. In 17 instances in each of the iodixanol groups the level of confidence in the radiological diagnosis was increased.

Study Report 1966 - Cranial Computed Tomography

This multicentre study was conducted in the US between January 1994 and June 1995. The seventy-five patients enrolled were stratified by age into those aged 0 - < 3 years and those aged 3 - ≤ 12 years.

Variations from the previously described study design were:

1. For assessment of efficacy, adequacy of enhancement a yes/no answer was required to the question: "Is the overall quality of enhancement adequate to make a radiographic diagnosis?
2. Haematology, blood chemistry and urinalysis were evaluated pre-and post-injection. Urea nitrogen and serum creatinine were assessed at three days post-injection when possible. The laboratory parameters were assessed using a 5 point scale: 1 = above/below reference range but not clinically relevant; 2 = clinically relevant but probably due to concurrent medication: 3 = clinically relevant, probably due to study drug: 4 = clinically relevant, due to disease state; 5 = clinically relevant, cause unknown. For each laboratory parameter and time point the following were reported

- Changes greater than 40% or greater than 80% of the span of the reference range
- Values outside the reference range
- Post-injection values that were considered both changes greater than 80% of the span of the reference range and outside the reference rage
- Actual numeric changes from baseline over time

Protocol amendments included the following (the timing in relation to the commencement of the study was not detailed):

Amendment-02 was to remove enrolment of patients > 12 year of age and to alter age stratification from 0 - < 12 and 12 – 18, to 0 - < 3 years and 3 = ≤ 12 years. From comment later in the text, it would appear that this amendment occurred after the commencement of the study.

Protocol Deviations

Patients who were enrolled in the trial prior to the implementation of Amendment A-02 had their ID numbers assigned from the initial randomisation codes for the two age group of 0 - < 12 and 12 to <18 years of age. Evidently the change left some children in the age group 3 to < 12 years included in the revised group 0 to < 3 years. None of the randomisation codes that had already been assigned were later changed. The numbers of individuals involved were not stated.

One child was assigned the randomised code number of another concurrent Visipaque paediatric protocol. Some patients did not have all vital signs and/or laboratory data reported.

Dosing and CT Scanning Procedures

For each single intravenous injection, the recommended dose was 2.0 mL/kg with a range of 1.0 - 2.0 mL/kg administered at room temperature or warmed to body temperature (37°C). Premedication was given according to hospital routine.

Statistical Methods

Data were pooled across centres. Statistical tests were all two-sided with significance set at 0.05. There were no adjustments for multiplicity. All patients who received any amount of study drug were included in the safety and efficacy analyses. No subsets were formed. Continuous variables were analysed using analysis of variance. Categorical variables were analysed using extended Fisher's exact tests. Kruskal-Wallis analysis was applied to outcomes based on ordered categories. Descriptive statistics were also planned and scatter plots generated.

Efficacy Results

A total of 75 patients were enrolled. There were no drop-outs.

- VIS-270: 23 patients
- VIS-320: 27 patients
- Iohexol 25 patients

The mean ages were; VIS-270: 5.82 years; VIS-320: 5.66 years; iohexol 5.87 years. Forty-eight percent were Caucasians and 47% were Black.

Ninety-five percent of patients were administered the study drug at room temperature. All patients received the trial drug as a single intravenous injection. The mean total doses administered were VIS-270: 0.47 g I/kg mean volume 39.41 mL; VIS-320: 0.65 g I/kg mean volume 44.60 mL; Iohexol 0.55 g I/ kg mean volume 45.48 mL.

Good or excellent quality of contrast enhancement overall was reported for 23/23 of the VIS-270 group, 26/27 for the VIS-320 group and 25/25 for the Iohexol group (Table 8). In one patient, enhancement did not occur due to extravasation of the study drug. For one patient in the VIS-270 group had poor enhancement of the pituitary stalk despite enhancement of all other areas rated as good or excellent. Detailed enhancement ratings are shown in Table 9. In the majority of cases in each of the iodixanol groups the level of confidence in the radiological diagnosis was increased (Table 10).

Table 8 Study Report 1966 Summary of Overall Contrast Agent Quality of Enhancement Results, N (%)

Quality of Enhancement[a]		VIS-270 (N=23)	VIS-320 (N=27)	OMN-300 (N=25)
Nondiagnostic (N=1)	Inadequate	0	1 (4)	0
Diagnostic (N=74)	Poor	0	0	0
	Good	4 (17)	3 (11)	1 (4)
	Excellent	19 (83)	23 (85)	24 (96)

[a] Quality of enhancement rating scale: Inadequate = 0; Poor = 1; Good = 2; Excellent = 3.
Fisher's exact test (2-tailed): diagnostic vs. nondiagnostic across groups, p=1.000.
Krusai-Wallis test: quality of enhancement ratings across groups, p=0.314.

Table 9 Study Report 1966 Summary of Radiographic Enhancement Rating

	VIS-270			VIS-320			OMN-300		
Visualization Area	N[b]	Good	Excellent	N[b]	Good	Excellent	N[b]	Good	Excellent
Cerebral arteries	23	4 (17)	19 (83)	27	3 (11)	23 (85)	25	0	25 (100)
Circumventricular organs	22	10 (45)	12 (55)	27	9 (33)	17 (63)	25	9 (36)	16 (64)
Venous sinus	23	2 (9)	21 (91)	27	0	26 (96)	24	1 (4)	23 (96)
White/gray junction	22	6 (27)	16 (73)	27	4 (15)	22 (81)	25	4 (16)	21 (84)
Other:									
ICEV[c]	0	0	0	0	0	0	1	0	1 (100)
PITS[d]	4	1 (25)	2 (50)	6	0	5 (83)	5	1 (20)	4 (80)

[a] Good = sufficient contrast enhancement; Excellent = superior contrast enhancement.
[b] N = the number of patients who had a particular area visualized.
[c] ICEV = intracerebral veins.
[d] PITS = pituitary stalk.

Table 6 Study Report 1966 Summary of Contribution of Contrast Agent to Radiographic Diagnosis, N (%)

Contribution of Contrast Agent	VIS-270 (N=23)	VIS-320 (N=27)	OMN-300 (N=25)
Increased confidence in diagnosis	21 (91)	24 (89)	22 (88)
Increased border definition	5 (22)	2 (7)	7 (28)
Differential enhancement of a mass	1 (4)	0	3 (12)
Other	2 (9)	1 (4)	1 (4)

[a] A patient may have had more than one type of contrast agent contribution.

Trial DXV038 - Computed Tomograph Scanning of Body

This study was performed at a single centre in Norway between May 1994 and October 1995. The age limits for this study were 1 month to < 13 years. Sedative premedication was allowed. The study contrast medium was injected intravenously. When oral and/or rectal contrast medium were needed, diluted iohexol 300 mg I/mL was used: 1 mL iohexol in 50 mL fluid, a concentration of 6 mg I/mL.

In addition to characteristics common to each or these studies, inpatients in this study were also evaluated by recording:

- Distress in patients capable of reporting discomfort
- Clinical chemistry parameters
- When possible, a blood sample was drawn before injection of contrast medium and at 3, 4 and 16 – 32 hours after the injection of contrast medium. Urine was to be collected before injection (either spot urine or collection during a time period) and at 3 hours and between 16 – 32 hours after the injection. After 2 months, creatinine and β2-microglobulin were measure in serum and urine in addition to N-acetylglucoseaminidase (NAG), alkaline phosphatase (ALP) and albumin (in urine only).

Protocol deviations were reported. The protocol stated that 75 Phase III patients were to be included. However the trial was stopped after 67 patients were included: 22 in each of the iodixanol groups and 23 in the iohexol group. Two patients in the VIS-270 group were outside the required age limit: one was 21 days old; the other was 13 years and 3 months.

The protocol was reported not to have been followed for three in the iohexol group due to: technical problems with equipment; incorrect dose; nausea and vomiting. In the VIS-320 group one patient was difficult to sedate.

Efficacy Results

All except two patients were Caucasians. The main referring diagnoses were tumours in different organs. The groups were reasonably well balanced for the demographic characteristics listed. The standard deviations for mean ages and weights were large.

The total volume of injected contrast agent was between 6 and 84 mL for VIS-270, 11 and 74 mL for VIS-320 and 11 and 84 for iohexol. The maximum amount of iodine administered per kg was 0.56 g in the VIS-270 group, 0.66 g in the VIS-320 group and 0.61 g in the iohexol group.

A large number of areas of the body were scanned. For overall diagnostic information all results were recorded as excellent or good except for one result in the iohexol group reported as poor due to technical problems (Table 11).

The contrast agent contributed to the diagnosis (by increased confidence or increased border definition) and provided additional information in the majority of cases.

Table 7 Trial DXV038 Efficacy Results – Overall Diagnostic information

PARAMETER		Iodixanol 270 mgI/ml	Iodixanol 320 mgI/ml	Iohexol 300 mgI/ml
OVERALL DIAGNOSTIC INFORMATION	Excellent	21	18	20
	Good	1	4	2
	Poor	0	0	1
	Inadequate	0	0	0
REASON FOR POOR OR INADEQUATE INFORMATION	Contrast density	0	0	0
	Movement	0	0	0
	Technical	0	0	1
	Other	0	0	0

STUDY REPORT 1967 - Computed Tomograph Scanning of Body

This was a multicentre study conducted in the United States between 08 February 1994 and 06 December 1994. The age limits for this study were from birth to 12 years of age. Participants were stratified by age. The original age groups of 0 to < 12 years and 12 to > 18 years were changed to 0 to < 3 years and 3 to 12 years according to protocol amendment A-02. Tumour mass, infection, abscess, inflammation and trauma were amongst the commonest referring diagnoses.

Protocol Deviations

Patients who were enrolled in the trial prior to the implementation of Amendment A-02 had their ID numbers assigned from the initial randomisation codes for the two age group of 0 - < 12 years and 12 to <18 years of age. Evidently the change left some children in the age group 3 to < 12 years included in the revised group 0 to < 3 years. None of the randomisation codes that had already been assigned were later changed. The numbers involved were not stated. One child was assigned the randomised code number of another concurrent Visipaque paediatric protocol.

Two additional patients at one centre received oral contrast after obtaining verbal consent but were not randomised to receive intravenous administration of the study contrast agent. The parent refused to sign the consent form for one patient, and for the other the blood samples required were not obtained.

Some patients did not have vital sign and/or laboratory data reported for all parameters at all time points specified in the protocol. At some sites, deviations in examination times occurred.

Two patients were enrolled in violation of the protocol inclusion or exclusion criteria

- One patient had two angiographic procedures with iohexol 300 g I/mL within eight hours of the CT body scan.
- Written informed consent was not obtained for one patient, however verbal consent was obtained and documented prior to the conduct of the study procedures.

The report stated that there was no evidence that the deviations compromised patient safety or the conclusions drawn from the trial.

Efficacy Results

Seventy-nine patients were enrolled and completed the trial.

- *VIS-270 Group* – 27 patients, mean age 5.19 years, mean weight 20.5 kg, mean total volume 37.38 mL, mean dose/ kg body weight 0.50 g I/kg
- *VIS-320 Group* – 26 patients, mean age 4.87 years, mean weight 18.84 kg, mean total volume 35.12 mL, mean dose/kg 0.61 g I/kg
- *Iohexol* – 27 patients, mean age 5.56 years, mean weight 20.97 kg, mean total volume 40.15 mL, mean dose 0.58 g I/kg

Approximately two thirds of each group was Caucasian. Contrast agent was administered at room temperature for 65/79 of the patients. Five patients, one in the VIS-270 Group, 3 in the VIS-320 group and one in the iohexol group were administered two intravenous injections. The remaining patients received a single injection. Fifty-nine patients received oral iohexol in conjunction with the intravenous study agent.

The results were reported as excellent or good for all patients in the VIS-270 Group, 23/26 patients in the VIS-320 Group and 26/27 in the iohexol group (Table 12).

Two patients in the VIS-320 Group had an evaluation that was non-diagnostic. One patient was administered 1 mL/kg bolus contrast instead of 2 mL/kg for scans of liver and inferior vena cava, and the rate of administration was considered poor. One patient had a slow rate of infusion due to mechanical limitations and interference from an artefact resulting in poor scan results for inferior vena cava, liver, spleen, pancreas and kidney.

Table 8 Study Report 1967

Summary of Overall Contrast Agent Quality of Enhancement Results, by Group, N (%)

Quality of Enhancement[a]		VIS-270 (N=26)	VIS-320 (N=26)	OMN-300 (N=27)
Nondiagnostic (N=2)	Inadequate	0	2 (8)	0
Diagnostic (N=77)	Poor	0	1 (4)	1 (4)
	Good	14 (54)	5 (19)	15 (56)
	Excellent	12 (46)	18 (69)	11 (41)

[a]

For diagnoses of tumour, trauma, infection/abscess/inflammation, the majority of scans either confirmed or ruled out the referring diagnosis and contributed positively to the diagnosis.

Study DXV036 Angiocardiography

Phase II

Subjects on this open pilot study which aimed to generate preliminary safety data were administered iodixanol 320 mg I/mL (VIS-320).The study included 10 out of the 13 planned patients, three of whom were aged between 2 and 5 years and seven of whom were aged between 1 week and 2 years of age The patients received a mean volume of 42 mL VIS-320, a dose of 1.32 g I/kg body weight.

Efficacy Results

Eight of the ten patients were Caucasians, two were African black. Five were male and five female, the age range was 5 months to 4 years 1 month. Seven were less than 2 years of age. The weight range was from 6 kg to 21 kg.

Results were evaluated by two investigators reaching a consensus in Centre 1, but by one investigator only at Centre 2. The overall quality of visualisation was judged to be excellent for all patients in the Phase II studies.

Phase III

This was a multicentre study conducted in Belgium between March 1994 and July 1995. Seventy eight patients were randomly assigned to receive either VIS-320 or iohexol 350 mg I/mL. Randomisation in this study was 2:1, iodixanol: iohexol.

The age limits for this study were initially from birth to less than 13 years of age but were changed to an upper limit of less than 16 years in a protocol amendment dated 10 November 1995,(that is, after the commencement of the study). Exclusion criteria particular to this study included weight lower than 2000 g, haemodynamic or respiratory signs related to premature birth, and scheduled for interventional catheterisation.

The most common indications were ventricular septal defect, atrial septal defect, tetralogy of Fallot, single ventricle and valvular incompetence. Cyanosis and symptoms of congestive heart failure were more often described in the iodixanol group, 38% and 25% respectively, compared to the iohexol group, 19% and 12% respectively.

Vital signs were recorded before and after each injection. A three-lead ECG was monitored continuously throughout the examination. Intravascular haemodynamic parameters were measured in the injected ventricle or vessel immediately before and for up to 120 seconds after each injection. Transcutaneous oxygen saturation was measured using pulse oximetry for up to 120 seconds after each injection.

Results

A total of 78 patients were enrolled; all were Caucasian

VIS-320 group included 52 patients (17 females and 25 males). In this group, 26 (50%) were less than 2 years of age (11 females and 15 males). In the iohexol group of 26 patients (11 females and 15 males), 8 (31%) were less than 2 years; two were less than 2 months of age.

The total volume injected was between 8 and 159 mL of iodixanol, the mean was 52.2 mL corresponding to mean 1.38 g I/kg. the total volume of iohexol 350 mg I/mL was between 17 and 160 mL, mean volume 61.3 mL corresponding to mean 1.39 g I/kg. The maximum amount of iodine administered per kg was 3.75 g (11.1 mL) in the iodixanol group and 2.72 g (7.8 mL) of iohexol. The majority of patients received less than 2.5 g I/kg (7.5 mL).

Results were evaluated by two investigators reaching a consensus in Centre 1, but by one investigator only at Centre 2. The overall quality of visualisation was judged to be excellent for all patients in the Phase III studies.

Study Report 1968 – Angiocardiography

This was a multicentre study conducted in the United States between January 1994 and August 1995. As with the preceding cardioangiography study DXV036, patients were stratified by age and randomly assigned to receive either VIS-320 or iohexol 350 mg I/mL. A total of 118 paediatric patents referred for contrast-enhanced angiocardiography were

enrolled; 117 patients were dosed. Patients were divided into two groups: 58 in the VIS-320 group and 57 in the iohexol-350 group.

The initial protocol which included patients > 28 days to < 18 years of age was amended to include patients from birth to 12 years inclusive,≥ 36 weeks gestation to > 2000 g of body weight. The age stratification criteria were changed from > 28 days to < 12 years of age and 12 to < 18 years of age to 36 weeks gestation to < 3 years and 3 years to 12 years at an unspecified time (Protocol revisions A-01 and A-03)

Premedication was given according to hospital routine prior to the administration of contrast agent. Patients were administered the contrast agent at room temperature for 24 patients or warmed to 37° C for 93 patients. The femoral vein was the injection catheter route most frequently used (78% of patients in the VIS-320 group and 75% in the iohexol 350 group). The femoral artery injection catheter route was used for 60% of the VIS-320 group and 66% of the iohexol 350 group. The dosage was based on the product monograph for iohexol 350

Laboratory parameters: for patients ≤ 28 days, total serum bilirubin, serum electrolytes and osmolality, serum bicarbonate or lactic acid were assessed at 4 to 8 hours post-injection, urine osmolality was assessed at 16 to 32 hours post-injection when possible. Serum creatinine and blood urea nitrogen were assessed between 40 to 56 hours post-injection. In addition, urine output was observed for post-injection changes.

Protocol Deviations were reported:

- Verbal consent only was obtained for three patients.
- One patient was unblinded at the request of the investigator. The patient died following repair of tetralogy of Fallot.
- For some patients vital sign or laboratory data were not collected, incorrectly collected, or had to be repeated.

Results

Of the 117 patients, approximately three quarters in each group were Caucasian. There were 61 males and 57 females. The mean ages were 2.14 years in the VIS-320 group and 2.07 years in the iohexol 350 group. The range was from 1 day to 10.60 years. Seventeen patients in each group were neonates, ≤ 28 days of age.

The mean total doses were 1.68 g I/kg and 1.80 g I/kg for the VIS-320 group and the iohexol 350 respectively. Mean total volumes injected were 49.83 mL and 42.27 mL respectively. The mean injection times were 4.11 seconds and 3.22 seconds respectively.

The mean total doses based on body weight for different age groups were as follows:

- VIS-320: 0 - ≥ 28 days, 29 days to < 3 years, 3 to 12 years - 1.62, 1.88 and 1.46 g I/kg
- Iohexol 350: 0 - ≥ 28 days, 29 days to < 3 years, 3 to 12 years - 1.75, 2.03 and 1.46 g I/kg

The mean total volumes based on body weight for different age groups were as follows:

- VIS-320: 0 - ≥ 28 days, 29 days to < 3 years, 3 to 12 years - 5.06, 5.88 and 4.56 mL/kg
- Iohexol 350: 0 - ≥ 28 days, 29 days to < 3 years, 3 to 12 years - 4.99, 5.79 and 4.17 mL/kg

Efficacy Results

Overall quality of visualisation was rated good or excellent for almost all patients in both the VIS-320 group and the iohexol 350 group (Table 13). One patient in the iohexol 350 group

rated poorly for overall quality due to technical difficulty. Two patients in the VIS-320 group had visualisation rated as poor for a specific injection site: one because of catheter recoil in the aortic root and one due to malfunction of the power injector. The contrast agent contributed to the diagnosis (by increased confidence, increased definition or the provision of additional information) in the majority of cases (Table 14).

Table 9 Study Report 1968

Summary of the Number (%) of Patients Whose Radiographic Visualization was Rated by the Investigator as Good or Excellent,[a] by Injection Site and Group

Injection Site[b]	VIS-320			OMN-350		
	N[c]	Good	Excellent	N[c]	Good	Excellent
Left Ventricle	51	8	42	49	7	42
Right Ventricle	32	3	29	30	5	25
Aortic Root	18	8	10	23	4	18
Pulmonary Artery	13	2	11	14	1	13
Aortic Arch	16	6	10	9	1	8
Descending Aorta	5	0	5	10	1	9
Superior Vena Cava	8	1	7	5	1	4
Left Coronary Artery	8	1	7	5	3	2

[a] Good = sufficient contrast visualization; Excellent = superior contrast visualization.
[b] Includes only those sites used in ≥ 10% of patients.
[c] N = the number of patients who had an efficacy evaluation for that injection site.

Table 10 Study Report 1968

Summary of the Contribution of the Contrast Agent to the Ability to Make a Radiographic Diagnosis, N (%)

Contribution of Contrast Agent [a]	VIS-320 (N=58)	OMN-350 (N=59)
Increased confidence in diagnosis	49 (84)	48 (81)
Increased definition of heart chamber(s)	45 (78)	44 (75)
Increased definition of vascular structure(s)	45 (78)	47 (80)
Provided additional detailed anatomical information	29 (50)	30 (51)
Other	1 (2)	2 (3)

Study DXC060 - Gastrointestinal Examinations

This multicentre study was undertaken in the United Kingdom, Denmark and Norway between August 1998 and June 1999. The study included 154 paediatric patients for birth to < 16 years of age. The objectives were to assess radiographic efficacy and safety of Visipaque 150 mg I/mL and 320 mg I/mL compared to Omnipaque 140 mg I/mL and 300 mg I/mL

This study, and the following study DXC064 of paediatric gastrointestinal contrast imaging, share study design, endpoints and statistical methods.

Efficacy criteria were judged by one appointed investigator per trial centre and included quality of radiographic visualisation scored on a 100 mm Visual Analogue Scale (VAS).

The main variable was overall quality of radiographic visualisation. Overall evaluations of radiographic visualisation and diagnostic information were obtained on a Visual Analogue Scale. Radiographic visualisation was graded in a manner very similar to the preceding studies:

Excellent	Superior radiographic visualisation. Very detailed radiographic delineation
Good	Sufficient radiographic visualisation. Adequate delineation
Poor	Insufficient radiographic visualisation. Inferior delineation
No visualisation	No visualisation of contrast in the region of interest

The degree of contrast opacification was evaluated as too high, optimal to low density or none. The coating of mucosa was scored in categories poor, good and excellent.

Safety variables were adverse events up to 2 days after the examination and any occurrence of bronchial aspiration (yes/no). Taste acceptance was also reported as good, acceptable, unpleasant and bad.

Severity of AEs was graded as mild, moderate and severe, as judged by the investigator based on his/her previous clinical experience with similar symptoms. A serious adverse event (SAE) definition was not included. Significant adverse events were defined as those non-serious AEs that had a marked haematological or other laboratory abnormality or any AE that lead to an intervention including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy.

Included were patients from birth to 16 years with written informed consent. Excluded were patients previously included in the trial or simultaneously participating in a drug administration phase of another clinical trial, those with previous serious reactions to iodinated contrast media, patients who were clinically unstable or were pregnant of breast feeding.

Study Population

A total of 154 patients were enrolled. One patient did not receive any test drug and one patient was withdrawn due to lack of recorded efficacy or safety data.

Seventy four patients received iodixanol; 79 received iohexol. The numbers receiving high and low dose of each could not be ascertained.

The safety population consisted of 152 patients. The efficacy population consisted of 147 patients: five patients were not included, one because of insufficient volume of contrast administered and four due to mixing with too high amounts of fruit juice.

Contrast Agents

- *Test product:* Visipaque 150 mg I/mL (VIS-150), Visipaque 320 mg I/mL (VIS-320)
- *Reference product:* Onmipaque 140 mg I/mL, Omnipaque 300 mg I/mL

Patients were randomised to four contrast medium groups to receive either high or low dose of test or reference product. Patients were stratified so that those referred for follow-through examinations would enter the higher concentration groups; most other patients were to be entered into the low dose groups.

Statistical Methods

The null hypothesis claimed equality in the mean score between the two treatment group, both overall and within high and low concentrations.

The underlying assumptions of normally distributed scores on the VAS were to be evaluated through plots and the Shapiro-Wilk's test. If the assumptions were reasonably fulfilled, an analysis of variance (ANOVA) would be performed in order to compare the mean scores of the two contrast groups. The analysis would, if possible, take into account the different concentration, age of the patients, an eventual centre effect and whether the scores varied between different types of examinations and diagnoses. If no such main effects or interactions were present, the final analysis was to be made by a two-sample t-test. The associated 95% CIs for the difference in mean score between the two contrast medium groups was calculated.

If the assumption of normality was not fulfilled, transformation of the observation or appropriate non-parametric tests would be performed. The level of significance was set to 5%

The sample size was based on the assumption that the standard deviation would approximate 15 mm and the difference between groups would be about 7.5 mm. The difference of 7.5, equivalent to 7.5% of the length of the scale, was considered to maybe have clinical significance and that a difference of 5 mm would be of no clinical importance.

Demographic Characteristics

All but 8 patients were Caucasian, 3 were Asian, 4 were Multiracial and 1 was Other. Mean age was 5.8 years in the iodixanol group. Mean age was 6.4 years. Mean weight was 21.9 kg in the iodixanol group and 25.4 kg for iohexol group.

Some patients had more than one indication for the procedure. The most frequent indications were: repeated vomiting (38 in the iodixanol group and 40 in the iohexol group) and abdominal pain (9, 13).

Efficacy Results

Iodixanol: 74 patients were included in the iodixanol group safety analysis; 71 were included in the efficacy analysis
Iohexol: 78 patients were included in the iodixanol group safety analysis; 76 were included in the efficacy analysis.

Examinations performed were:

Upper GI series: iodixanol 52, iohexol 55
Oesophagus: iodixanol 20, iohexol 16
Follow-through examination: 15 in each group
Ostomy studies: iodixanol 4, iohexol 1
Enema: iodixanol 4, iohexol 9

One patient was given barium due to poor contrast with the trial drug (iohexol 140 mg I/mL). Four cases required continuing the x-ray examination with barium after use of the iodinated contrast medium had confirmed that there was no risk to the administration of barium. Images taken after administration of barium were not included in the efficacy evaluations.

Mean volume of contrast ingested was 84.74 mL for patients in the iodixanol group and 91.50 mL of patients in the iohexol group. Patients in the iodixanol group received a higher dose of iodine per kg body weight compared to the iohexol group.

In the analysis of the main endpoint, the adjustments for dose and volume administered were not done. The volume actually retained by the patient was difficult to estimate due to dribbling, coughing and so on.

In the efficacy evaluations of different areas (visualisation and coating), there was a difference between trial centres in how the categories were used. Therefore these data were not pooled.

No difference between the two contrast medium groups was observed. Visualisation quality is shown in Tables 15, 16 and 17. The VAS score for iodixanol was 86.28 compared to that for iohexol 82.43, the difference 3.85 with 95% CI (-2.56, 10.42). The evaluator was concerned that treated patients were excluded for a reason not specified in the protocol. It was not apparent from which group these patients were excluded.

In no case was contrast medium observed in the bladder after gastrointestinal examination.

Table 11 Quality of Radiographic Visualisation presented per contrast medium group– Efficacy Population (number of patients)

DRUG	AREA	Quality of radiographic visualization					
		Excellent	Good	Poor	Not visualized	Not applicable	TOTAL
Iodixanol	Oesophagus	19	24	7	4	17	71
	Stomach	32	25	3		11	71
	Duodenum	21	28	6		16	71
	Jejunum	14	15			42	71
	Ileum	12	6			53	71
	colon ascendum	9	4		2	56	71
	colon descendum	4	3			64	71
	colon transversum	3	2	1	2	63	71
	Rectum	4	2			65	71
Iohexol	Oesophagus	25	21	13	1	16	76
	Stomach	33	24	5	1	13	76
	Duodenum	21	26	9	2	18	76
	Jejunum	15	13	2	1	45	76
	Ileum	11	4			61	76
	colon ascendum	7	4		5	60	76
	colon descendum	7	3		2	64	76
	colon transversum	5	1	1	4	65	76
	Rectum	5	5			66	76

Table 12 Study DXC060 – Quality of Radiographic Visualisation presented per concentration of contrast medium – Efficacy Population (number of patients)

DRUG	AREA	Quality of radiographic visualization					TOTAL
		Excellent	Good	Poor	Not visualized	Not applicable	
Iodixanol 150 mgI/ml	Oesophagus	12	15	6	3	11	47
	Stomach	17	19	2		9	47
	Duodenum	11	17	5		14	47
	Jejunum	8	8			31	47
	Ileum	6	2			39	47
	colon ascendum	5	1		2	39	47
	colon descendum	2	2			43	47
	colon transversum	1	1	1	2	42	47
	Rectum	2	2			43	47
Iohexol 140 mgI/ml	Oesophagus	11	15	10	1	11	48
	Stomach	14	19	5	1	9	48
	Duodenum	9	17	7	2	13	48
	Jejunum	9	4	2	1	32	48
	Ileum	6	3			39	48
	colon ascendum	3	3		3	39	48
	colon descendum	5	2		2	39	48
	colon transversum	4		1	3	40	48
	Rectum	4	4			40	48

Table 13 Study DXC060 Quality of Radiographic Visualisation presented per concentration of contrast medium – Efficacy Population (number of patients)

DRUG	AREA	Quality of radiographic visualization					TOTAL
		Excellent	Good	Poor	Not visualized	Not applicable	
Iodixanol 320 mgI/ml	Oesophagus	7	9	1	1	6	24
	Stomach	15	6	1		2	24
	Duodenum	10	11	1		2	24
	Jejunum	6	7			11	24
	Ileum	6	4			14	24
	colon ascendum	4	3			17	24
	colon descendum	2	1			21	24
	colon transversum	2	1			21	24
	Rectum	2				22	24
Iohexol 300 mgI/ml	Oesophagus	14	6	3		5	28
	Stomach	19	5			4	28
	Duodenum	12	9	2		5	28
	Jejunum	6	9			13	28
	Ileum	5	1			22	28
	colon ascendum	4	1		2	21	28
	colon descendum	2	1			25	28
	colon transversum	1	1		1	25	28
	Rectum	1	1			26	28

Study DXC064 Gastrointestinal Examinations

This study was undertaken in two centres in Sweden between 15 January 1997 and 28 May 1998. The study included paediatric patients for birth to < 16 years of age. Patients were required to be conscious and cooperative. Patients with weight lower than 1500 g were excluded as were patients diagnosed as having coexisting severe disease. Patients in a clinically unstable condition were allowed entrance into the study.

Patients were stratified by age to ensure sufficient numbers of patients less than 2 years of age, and randomised into four contrast medium groups. A total of 140 patients were planned however due to slow enrolment 112 patients were entered into the study.

The study drugs included iodixanol 150 mg I/ml and iodixanol 270 mg I/mL compared to iohexol 140 mg I/mL and 300 mg I/mL. The dose guideline was 5 mL/kg. In this study, rectal administration was excluded according to a protocol amendment that predated the onset of the study.

Results

There were 112 patients enrolled. One patient did not receive any test drug and was considered a drop-out from the trial. The safety population consisted of 111 patients. The efficacy population comprised 110 patients: images for one patient were lost.

All but nine patients were Caucasian, one was Oriental, two were African black, one was Multiracial, four were Other and one was unknown. The mean age was 3.7 years in the iodixanol group and 3.6 years in the iohexol group. The mean weight was 17.6 kg in the iodixanol group and 16.4 kg for iohexol group.

Some patients had more than one indication for the procedure. The most frequent indications were repeated vomiting and abdominal pain. The most often performed test was stated to be ventricle[1] (sic) examination, oesophagus examination and follow-through examination.

Efficacy

The mean VAS score for iodixanol was 71.61 mm and in the iohexol group 70.49. The 95% CI for the difference was (-5.28, 7.52). An effect of concentration was present (p = 0.001). Patients receiving the higher dose had higher VAS scores. An effect of centre was also significant (p = 0.0004). Centre 1 had lower scores than Centre 2.

Safety

Safety Results - Report 2493 Pharmacokinetic Study

All 43 patients were included in the safety analyses. All patients received Visipaque Injection 320 mg I/mL (VIS-320) which was administered at room temperature to 29 patients and at body temperature to 14 patients. Overall the mean dose of VIS-320 was 1.49 g I/kg. The mean total volume was 4.67 mL/kg. The mean duration of the procedure was 30 minutes and the mean number of procedural injections was 2.7.

All patients received one or more premedications or procedural medications. The most commonly used were central nervous system drugs; 41/43, received some level of sedation for their procedure. Cardiovascular drugs were administered to 74% and haematological drugs to 61%

Adverse Events

[1] This word was also used in tables; perhaps arose from the use of a language other than English.

A total of 34 adverse events (AEs) were reported for 18 of the 43 patients (42%) (Table 18). No AE was reported to be related to the study drug.

AEs reported from more than 1 patient included vomiting (5 out of 43 patients) (12%), anaemia (4) (9%), atelectasis (3) (7%), nausea (3) (7%), hypokalaemia (2) (5%) and injection site pain (2) (5%). Ten patients were evaluated for observer reports of injection-associated discomfort/distress and no cases were reported.

Table 18: Study Report 2493

Summary of Adverse Events Other Than Injection-Associated Discomfort/Distress, N (%)[a]

Adverse Event (WHO Preferred Term)	Age Group					Combined (N=43)
	<2 mo (N=8)	2 to <6 mo (N=9)	6 to <12 mo (N=10)	1 to <3 yr (N=8)	3 to ≤12 yr (N=8)	
Number of patients With AEs[b]	4 (50)	3 (33)	4 (40)	5 (63)	2 (25)	18 (42)
Total Number of AEs	12	3	4	9	6	34
Vomiting	0	1 (11)	1 (10)	2 (25)	1 (13)	5 (12)
Anemia	2 (25)	0	1 (10)	1 (13)	0	4 (9)
Atelectasis	2 (25)	0	0	1 (13)	0	3 (7)
Nausea	0	0	0	1 (13)	2 (25)	3 (7)
Hypokalemia	2 (25)	0	0	0	0	2 (5)
Injection site pain	0	0	1 (10)	0	1 (13)	2 (5)

[a] Adverse events occurring in more than one patient.
[b] A patient may have reported more than one adverse event.

One patient, a 27 month old girl with hypoplastic left heart syndrome died 27 days after the procedure because of acute renal failure complicated by sepsis. The events were not considered related to study drug. There were no other serious adverse events (SAEs) reported during the trial. Two SAEs were reported after the trial, one patient experienced a cardiac arrest 5 days after completing the study and another experienced lung atelectasis and collapse four days after completing the trial; neither was considered study product related. There were no discontinuations due to adverse events.

One patient experienced acute renal failure of severe intensity. All other AEs were mild or moderate in intensity.

Laboratory Tests

One day after the procedure, changes from baseline that were considered statistically significant were observed for the following parameters, but not considered clinically significant:

- Increase in chloride and neutrophils
- Decrease in blood urea nitrogen (BUN), eosinophils, haematocrit, haemoglobin, lymphocytes, platelets and red blood cells

Five patients had a total of nine clinically relevant changes in laboratory parameters reported as adverse events. All events were mild except for one patient with hypokalaemia and anaemia which were of moderate intensity. The events began 18 to 69 hours after the procedure and most events required some treatment. Three patients recovered, one patient's

AE of leucocytosis was ongoing when she died of renal failure, and one patient's status was unknown (lost to follow-up)

Compared to baseline values, two patients had increases in serum creatinine values above the reference range after the procedure. Four patients had increases in serum creatinine > 40% of the span of the reference range and one patient met both these criteria.

Vital Signs

There were no post-injection changes from baseline considered clinically relevant. None of the patients experienced clinically relevant changes in haemodynamic parameters. One patient experienced a clinically relevant change in ECG - premature atrial contractions of mild intensity that resolved in approximately 4 hours and were not considered to be related to study drug injection.

Conclusion Study Report 2493

The study sample size was too small for safety conclusions. The presence or absence of red blood cells in urine was not commented upon despite the findings in animal studies. The follow-up was relatively short. Lymphocytes were decreased for 46% of participants with results.

Randomised Controlled Trials

The safety results of these studies were presented separately in the submission despite the similarity of the study designs. The summary presented by the sponsor was too non-specific with regard to formulation to be considered useful in presenting a collated safety summary. The evaluator did not have access to the safety results in sufficient detail to undertake the fusion of results. Hence results are included in this report according to the study. In reporting relatedness of results, it could not be ascertained whether "uncertain" was meant to be understood as possibly related.

AEs in these studies were monitored for one day after dosage in the parenteral studies and 2 days for gastrointestinal use. Vital signs of blood pressure and pulse rate and injection-associated discomfort and distress were reported for all parenteral studies. For patients unable to report discomfort, distress was assessed by the investigators. Laboratory parameters were reported for Studies 4 – 8 and ECG and haemodynamics were recorded for the two angiocardiography studies. Occurrence of bronchial aspiration and taste acceptance were reported for the two GI studies.

AEs other than injection-associated discomfort/distress were reported as either related or not related to contrast medium and of mild, moderate or severe intensity. The relationship to the study drug was reported as: no, unlikely, unknown and likely.

Injection-associated discomfort and distress was assessed using a three-point scale (mild, moderate or severe). Discomfort was defined as a sensation of warmth, cold, pressure or pain related to the injection as reported by the patient. Distress was assessed behaviourally both for young children and patients unable to adequately verbalise.

Supine blood pressure and pulse were measured within 1 minute prior to injection, 2 – 3 minutes after the start of the injection and 20 – 30 minutes after completion of the injection.

A total of 901 infants and children aged between birth and up to 17 years were included in the studies; 321 were younger than 24 months. In total 534 patients received Visipaque and 376 received iohexol.

Phase II Studies

Study DXV041 – urography

The study included three female participants aged between 3 years 8 months and 4 years 7 months who were enrolled in the pilot study. Two patients were administered VIS-320 and one was administered VIS-270. The total volumes injected ranged from 30 – 35 mL. The patient who received VIS-270 had dose of iodine of 0.54 g I/kg. The patients who received VIS-320 each had a dose of 64 g I per kg body weight.

There were no adverse events reported and no changes in vital signs judged by the investigators to be clinically relevant noted in the Phase II component of this study. One patient reported pain of moderate intensity at the injection site. One patient reported injection-associated discomfort as pressure of moderate intensity.

Study DXV036 Angiocardiography

The study included 10 out of the 13 planned patients, three of whom were aged between 2 and 5 years and seven of whom were aged between 1 week and 2 years of age. The patients received a mean volume of 42 mL VIS-320, a dose of 1.32 g I/kg body weight.

Six adverse events other than injection-associated discomfort were reported by four patients, none of which were considered related to study drug. None of the patients reported injection-associated discomfort and no signs of distress were observed.

Phase III Studies

Study DXV041 Excretory Urography

Forty-seven of the 75 patients were judged able to report discomfort. Three of these patients reported discomfort, one in each contrast medium group. Two patients reported pain, one in the VIS-320 of moderate severity and one in the VIS-270 group of mild severity. One patient in the iohexol group reported a mild sensation of coldness. Injection-associated distress of mild severity was reported for four patients, two in the VIS-320 group, and one each in the other two groups. All were reported to be of mild intensity. Other AEs each reported by one patient in the VIS-320 group were vertigo, nausea and pruritus. Only pruritus was considered related to iodixanol. In the iohexol group one patient reported fever and exanthema. There were no deaths and no serious adverse events were reported. There were no changes in vital signs considered by the investigators to be clinically relevant.

Study DXV037 – Excretory Urography

Injection-associated distress was not reported for any patient. A total of 39 out of 72 patients were judged able to report discomfort. One of these patients reported a mild sensation of heat/warmth in the throat after injection of VIS-320. Other AEs each reported by one patient in the VIS-320 group were erythema, fever and periorbital oedema. Only periorbital oedema was considered related to iodixanol. In the iohexol group one patient reported pruritus considered to be related to the contrast medium. There were no deaths and no serious adverse events were reported.

There were no changes in vital signs considered by the investigators to be clinically relevant. One patient in the VIS-320 group had an increase in blood pressure from 80/40 to 120/90 thought to be associated with crying during the procedure.

Study DXV039 – Cranial Computed Tomography

Injection-associated distress of mild severity was reported for one patient in the VIS-270 group. The number judged able to report discomfort was not stated. A total of nine patients

reported injection associated discomfort, all of mild intensity. In the VIS-270 group, there was 1 report of pain and 3 of a sensation of heat. In the VIS-320 group, there were 2 reports of a feeling of cold and 1 of a sensation of heat. In the iohexol group: 2 reported a sensation of heat. Other AEs each reported by one patient in the VIS-320 group were tiredness and erythema, both of which were considered unrelated to iodixanol. In the VIS-270 group, 6 patients experience a total of 7 AEs, 5 of which were considered contrast-medium related: tiredness, nausea (two patients) smell perversion and metallic taste in mouth. Two were of uncertain relatedness: dry mouth, and urticaria. All were of mild intensity. In the iohexol group 3 patients reported four AEs: taste perversion of mild intensity was considered related, nausea of mild intensity and nausea and vomiting of moderate intensity were stated to be of uncertain relatedness. There were no reported deaths or serious adverse events.

Changes in vital signs of more than 10% from baseline were considered clinically relevant. Six patients in the VIS-270, 5 in the VIS-320 and six in the iohexol group were reported to have clinically relevant changes in vital signs. The change was an increase for all patients itemised. Without knowledge of the age of the children affected these results are difficult to interpret. For VIS-320 2 patients had changes in pulse and blood pressure and three in pulse rate. For VIS-270 4 patients had changes in pulse and blood pressure and one in blood pressure. For iohexol 2 patients had changes in blood pressure, 2 had changes in pulse rate and 2 had changes in both blood pressure and pulse rate.

Study Report 1966 - Cranial Computed Tomography

There were no deaths or serious adverse events were reported.

Eight of the 75 patients experienced injection associated discomfort: 3/23 in the VIS-270 group (one report each of heat, cold and pain); 1/27 in the VIS-320 group (heat) and 4/24 in the iohexol group (all reports of heat). The drug was administered at room temperature in all cases.

Four patients reported adverse events other than injection-associated discomfort/distress (Table 19). All were mild in intensity and none were considered by the investigator to be related to study drug although for one patient, pruritus and rash were consider of unknown relationship and for another patient pruritus and rash were considered unlikely to be related.

Table 19 Study Report 1966 Summary of Adverse Events

Adverse Event (WHO Preferred Term)	VIS-270 (N=23)	VIS-320 (N=27)	OMN-300 (N=25)
Number of patients with AEs[a]	1 (4)	2 (7)	1 (4)
Pruritus	0	2 (7)	0
Hemorrhage NOS	0	0	1 (4)
Nausea	1 (4)	0	0
Vomiting	1 (4)[b]	0	0
Rash	0	1 (4)	0
Rash maculopapular	0	1 (4)	0

[a] A patient may have experienced more than one adverse event.
[b] Investigator reported that patient 001-0156 was vomiting when he arrived in radiology and was treated with medications (as listed in Appendix 2.5.4) prior to contrast administration. Vomiting continued during the study and medications were continued.

The investigators considered that were no clinically relevant changes in vital signs or laboratory parameters reported. The largest individual change from baseline for systolic blood pressure was an increase of 45 mmHg for a patient in the VIS-320 group. This patient's systolic blood pressure had increased from a baseline of 106 to 151 mmHg at 1 hour post injection and had decreased to 122 mmHg at 1 day post-injection. The largest individual change from baseline for diastolic pressure was for another patient in the VIS-320 group. The diastolic pressure of 48 mmHg at baseline was 97 mmHg at 1 hour post-injection and had decreased to 75 mmHg at Day 1 recording. Although there may have been reasons for these changes that were not relevant to the injection, the evaluator finds it hard to consider that they were not clinically relevant.

Study DXV038 - Computed Tomograph Scanning of Body

One patient receiving VIS-270 reported a mild sensation of warmth in the mouth considered to be an injection-associated discomfort. Injection associated distress was reported for two patients, one of mild and one of moderate intensity. For other AEs, two patients administered VIS-270 experienced exanthema of moderate intensity and a bad taste in the mouth of mild intensity respectively, both of which were considered study drug related. For VIS-270, one patient experienced seven AEs (nausea x 2, itching x 2, increased sweating x 2 and vomiting). All events were of moderate intensity and were considered study drug related. For iohexol, two patients experienced three adverse events: feeling of warmth (mild intensity, relatedness uncertain), and nausea and vomiting (moderate intensity, related to study drug). There were no deaths reported.

Study Report 1967 - Computed Tomograph of Body

Three patients in the VIS-320 Group and two in the iohexol group experienced injection associated discomfort/distress; there was one investigator reported distress reported. The patients who reported discomfort were administered the contrast agent at room temperature. The patient who reported with distress received the contrast agent at body temperature.

Three patients administered VIS-270 experienced other AEs (Table 20). One severe adverse event report was of pulmonary fibrosis from which the patient died 6 days after the study procedure. The event was not considered study drug related. One patient experienced involuntary muscle contractions and shortness of breath of moderate intensity and was treated with calcium gluconate for a low calcium level.

For VIS-270, there were no AEs reported while for iohexol, one patient reported vomiting.

There were no changes in vital signs considered to be clinically relevant. There were no clinically significant abnormal laboratory values judged by the investigator to be related to study drugs. .

Table 20 Study Report 1967

Summary of Adverse Events, by Group, N (%)

Adverse Event (WHO Preferred Term)	VIS-270 (N=26)	VIS-320 (N=26)	OMN-300 (N=27)
Number of patients with AEs	3 (12)	0	1 (4)
Shortness of breath	1 (4)	0	0
Muscle contractions involuntary	1 (4)	0	0
Pruritus	1 (4)	0	0
Pulmonary fibrosis	1 (4)	0	0
Vomiting	0	0	1 (4)

Study DXV036 Angiocardiography

Eight of the 78 patients were judged able to report injection-associated discomfort. Two patients reported injection-associated discomfort, both a mild sensation of warmth. Injection-associated distress was observed in 3 patients.

Four or the ten pilot patients experienced six adverse events other than injection-associated discomfort/distress. Ten Phase III patients (19%) experienced 12 adverse events (vomiting x 4, fever x 2, leg pain, headache, metabolic acidosis, anaemia, asphyxia, coughing) in the iodixanol group and five (19%) (vomiting x 3, crying abnormal, pain) in the iohexol group. None of the events were considered related to contrast medium. No serious adverse event was reported.

Changes in systolic and diastolic blood pressure and pulse were reported to be small and not clinically relevant with no systematic difference noted between the two groups. Haemodynamic parameters measured at the injection site through the catheter and changes in oxygen saturation were not considered clinically relevant.

After injection into the aorta and into the left and right ventricles there was a general tendency noted for the QTc interval to increase, though the change was not considered clinically relevant.

The probable cause for arrhythmias was not reported (Table 21, Table 22). All arrhythmias reported were premature ventricular or atrial contractions. Most arrhythmias occurred after left ventricular injections in seven patients in the iodixanol group and four in the iohexol group. Six patients in the iodixanol group and none in the iohexol group had arrhythmias after right ventricular injections.

Table 21 Study DXV036 – Arrhythmias – Pilot Study

INJ. SITE GROUP	GROUP	Arrhythmias		No Arrhythmias	
		n	%	n	%
Aorta group	Iodixanol 320 mgI/ml	0	0	4	100.0
Pulmonalis group	Iodixanol 320 mgI/ml	0	0	4	100.0
Ventriculum left	Iodixanol 320 mgI/ml	2	28.6	5	71.4
Ventriculum right	Iodixanol 320 mgI/ml	1	20.0	4	80.0

Table 22 Study DXV036 – Arrhythmias after Injection Number of patients per injection site

INJ. SITE GROUP	GROUP	Arrhythmias		No Arrhythmias	
		n	%	n	%
Aorta group	Iodixanol 320 mgI/ml	0	0	18	100.0
	Iohexol 350 mgI/ml	1	7.7	12	92.3
Pulmonalis group	Iodixanol 320 mgI/ml	1	5.0	19	95.0
	Iohexol 350 mgI/ml	1	7.1	13	92.9
Venous group	Iodixanol 320 mgI/ml	0	0	7	100.0
	Iohexol 350 mgI/ml	0	0	3	100.0
Ventriculum left	Iodixanol 320 mgI/ml	7	20.6	27	79.4
	Iohexol 350 mgI/ml	4	22.2	14	77.8
Ventriculum right	Iodixanol 320 mgI/ml	6	18.8	26	81.3
	Iohexol 350 mgI/ml	0	0	12	100.0
Shunts	Iodixanol 320 mgI/ml	0	0	2	100.0
	Iohexol 350 mgI/ml	0	0	2	100.0
Other	Iodixanol 320 mgI/ml	0	0	6	100.0
	Iohexol 350 mgI/ml	0	0	1	100.0

NOTE: All arrhythmias were experienced before withdrawal of catheter.
No arrhythmias were recorded at centre 2.

Study Report 1968 – Angiocardiography

There were no reports of discomfort due to the youth of the patients and due to sedation. Two patients in the VIS-320 Group experienced a total of four episodes of injection-associated distress – 3 severe and 1 mild. Six patients in the iohexol 350 group experienced a total of 12 episodes of injection-associated distress: 11 mild and 1 moderate. All episodes were of short duration, of up to 2 minutes.

There were 4 deaths as summarised in Table 23 below.

Table 23 Study Report 1968 - Deaths

Group Patient ID	Adverse Event	Onset[a]	Duration	Intensity	Relationship to Trial Drug
VIS-320					
001-0181[b]	Sepsis[c]	14 days	13 days	severe	no
001-0184	MI[c] Sepsis[c]	4 days 4 days	1 day 11.5 hours	severe severe	no no
002-0209	Cardiogenic shock[c]	2 days	10 hours	severe	unlikely
OMN-350					
002-0210	Cardiogenic shock[c] DIC Acute renal failure	2.5 days 1 day <1 day	2 hours 2 days 3 days	severe severe severe	unlikely unlikely unlikely

MI=myocardial infarction, DIC=disseminated intravascular coagulation.
[a] Time from injection to onset of the adverse event.
[b] There were no adverse events recorded for this patient during the trial because the onset of the sepsis was 5 days prior to participation in the study; the sepsis did not worsen until 13 days after completion of the scheduled trial period.
[c] Adverse event(s) occurred after the patient completed all scheduled trial procedures (>30 hours postinjection).

Four patients in the VIS-320 group reported a total of 6 serious adverse events. SAEs included arrhythmia, necrotising enterocolitis, rash, acute renal failure and two reports of fever. Events were considered of unlikely relationship or of no relationship with the exception one episode of fever was of unknown relationship and the arrhythmia which was considered by the sponsor's medical safety officer to be possibly associated with the contrast agent. Three patients experience four serious adverse events which occurred post-study (more than 30 hours post-injection). These events included myocardial infarction, sepsis, cardiogenic shock and pneumonia. Two of the patients died as a result (Table 23). The death from sepsis of an additional patient 26 days after completing the trial was also reported.

Two serious adverse events were reported for one patient in the iohexol 350 group: disseminated intravascular coagulation and acute renal failure. This patient also experienced the serious adverse event of cardiogenic shock which occurred post-study. The events resulted in the death of the patient. All three events were considered unlikely to be due to the study drug.

Nineteen percent (11/58) of patients in the VIS-320 group reported a total of 18 adverse events and a similar percentage (11/59) in the iohexol 350 group reported a total of 14 adverse events. The only adverse events reported by more than one patient in either group were fever, vomiting and rash.

No trends in haemodynamic measurement were observed in changes from baseline measurement were reported. No clinically relevant change in urine output was observed for any neonate in either group.

Nine patients experienced at least one post-injection arrhythmia: 6 in the VIS-320 group and 3 in the iohexol 350 group. The most frequently reported arrhythmia in both groups was premature ventricular contractions which were reported following left ventricular injection of contrast agent. One patient in the VIS-320 group experienced atrial flutter which was considered a serious adverse event but which was considered by the investigator to be not related to study drug.

Two neonatal patients in the VIS-320 group had clinically relevant changes in oxygen saturation documented. One patient had clinically labile oxygen saturation levels before catheterisation.

Three patients, two in the VIS-320 group and 1 in the iohexol 350 group, had clinically significantly abnormal post-injection laboratory values that were judged by the investigator to be related to the study drugs: VIS-320: Increase in creatinine in one patient and increase in aspartate transaminase (AST)/alanine transaminase (ALT) in one patient; iohexol 350: an increase in AST/ALT.

The evaluator noted a decrease in lymphocytes of > 40% for 8 (22%) of the VIS-320 group and 10 (29%) of the iohexol 350 group, and a decrease of > 80% for 4 (11%) of the VIS-320 group and 2 (6%) of the iohexol 350 group with no increases of > 80% and 1 increase of > 40% in each group.

Study DXC060 - Gastrointestinal

Adverse events were reported for 12 patients in the iodixanol group and 28 patients in the iohexol group. The difference was mainly in the occurrence of diarrhoea (5 iodixanol and 23 iohexol patients). In some instances diarrhoea was present before the procedure. Nausea was reported for one patient in each group. Vomiting was reported for 3 patients in the iohexol group. Abdominal pain was reported for 2 patients in the iodixanol group. One patient in the VIS-320 group experienced rash fever and itching considered study drug related. Three patients in the iodixanol group had reported skin reactions. Bronchial aspiration was reported for 1 patient in each group. AEs considered study product-related were reported for 6 events in the iodixanol group and 5 in the iohexol group. For 9 events in the iodixanol group and 30 in the iohexol group relatedness was uncertain.

No deaths of serious adverse events were reported. There were no AEs leading to changes in dose or administration procedure, nor withdrawal from the trial.

Taste was not evaluated by 48 of the patients. Thirty-three scored the taste good, 36 acceptable, 19 unpleasant and 16 as bad. The addition of fruit juice did not appear to improve the taste acceptance.

Study DXC064 Gastrointestinal

No deaths or serious adverse events were reported. There were no AEs leading to changes in dose or administration procedure, nor withdrawal from the trial. All AEs were mild or moderate in intensity. Adverse events were reported for 21 patients in the iodixanol group and 27 in the iohexol group. Diarrhoea was reported for 16 in the iodixanol group and 21 in the iohexol group. One patient in the iohexol reported skin rash. On episode of bronchial aspiration in the iohexol group was the only AE considered study drug related.

In one case ‘a little’ contrast medium could be observed in the bladder. In many instances the bladder was not included in the field of examination.

The addition of fruit juice made the examination possible to perform in patients who refused due to the taste.

Literature search

A number of case reports included in the submission were not summarised by the evaluator as they were not considered to add new information. Similarly, reports that were basically review articles are also not summarised by the evaluator. The main emphasis in including the following publications is safety.

The aim of the study by Cullen et al was to investigate the value of serial arteriography to assess tumour response, predict necrosis and individualise the duration of a combined intravenous and intra-arterial neoadjuvant chemotherapy protocol in patients with biopsy-proven high-grade osteosarcoma or malignant fibrohistiocytoma of bone.[2] Contrast agent used included sequentially as the study progressed: Conray 60 (iothalamate meglumine), Isovue 300 (iopamidol) and after 1995, Visipaque 320.

One hundred and nine patients underwent a total of 408 intra-arterial procedures. Three minor complications and no major complications were considered related to arteriography (though not stated to be directly related to contrast agent). One patient experienced painful arterial spasm, two patients developed minor haematomas. The arteriogram correctly predicted a good histological response in 86 of 89 patients and correctly predicted a poor outcome in 12 of 20 patients: sensitivity 97%; specificity 60%.

One of the articles reviewed was a report of Study DXV-037.[3] Another was a report of the study identified as Study Report 2493.[4] A further report was based on Study DXC060.[5]

A study by Jeinin et al was a retrospective study including 115 paediatric patients with congenital heart disease. In these patients image enhancement had been attained using Visipaque 320.[6] The electron beam angiography was performed without complications in all patients.

A report by Lidegran et al included patients treated with extracorporeal membrane oxygenation for a variety of respiratory indications.[7] Patients ranged in age from neonates to adults. Of the 112 patients, 46% underwent CT examinations and 52% of these used contrast agent (Visipaque 270). It was not possible to determine the numbers receiving contrast agent by age. However it was stated that none of the patients had reported complication related to the procedure.

In Popova et al, the authors cited literature references to findings of cytogenetic analysis of in vitro cell cultures exposed to diagnostic doses of x-rays and contrast media.[8] Parallel clinical investigations showed an increased genotoxicity in the peripheral blood lymphocytes of patients undergoing angiography. The results indicated that some contrast agents can induce

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[2] Cullen JS, Brandt A et al. The value of serial arteriography in osteosarcoma: delivery of chemotherapy determination of therapy duration and prediction of necrosis. J Vasc Interv Radiol 2005; 16: 1107-1119.

[3] Dacher J-N, Sirinelli D et al. Iodixanol in paediatric excretory urography: efficiency and safety compared to iohexol. Pediatr Radiol 1998; 28: 112–114.

[4] Johnson WH, Lloyd TR et al. Iodixanol pharmacokinetics in children. Pediatr Cardiol 2001; 22: 223 – 227.

[5] Wright NB, Carty HML et al. Iodixanol in paediatric gastrointestinal imaging: safety and efficacy comparison with iohexol. Br J of Radiology 2002; 75: 127 – 135.

[6] Jeinin V, C J et al. Three dimensional CT angiography for patients with congenital heart disease: scanning protocol for pediatric patients. Catheter Cardiovasc Interv 2006; 67: 120-126.

[7] Lidegran M, Palmér K et al. CT in the evaluation of patients on ECMO due to acute respiratory failure. Pediatr Radiol 2002; 32: 567 – 574.

[8] Popova L, Hadjidekova V et al. Cytogenetic analysis of peripheral blood lymphocytes after arteriography (exposure to x-rays and contrast medium). Radiol Oncol 2005; 39: 153 – 158.

genotoxic effects alone but in combination with X-rays the radiation may increase, even double, the radiation induced genetic damage. Radiological contrast media do not only increase the absorbed dose, but may also enhance the sensitivity of blood cells to the radiation-induced cell damage.

The study included 29 patients, only two of whom received iodixanol (320), both of whom were adults and both underwent cranial CT. There were seven patients in total undergoing cerebral arteriography and none were shown to have an increase in the frequency of chromosomal aberrations.

In Wang et al extravasations were reported to occur in 475 (.07%) of the 69 657 patients included in this retrospective study.[9] Follow-up information was available for 442 adults and 17 children. Iodixanol was implicated in 12 cases (3%). Extravasated volumes ranged from 3 to 150 mL. Symptoms usually consisted of swelling and/or pain. Plastic surgery referral was required by 38 adults and 6 children, treatment being required for 7 adults and 1 child. Fifteen children had minimal or no adverse effects, one had moderate adverse effects and one had a severe complication after 18 mL of contrast material, iohexol, extravasated into the arm causing brachial plexus neuropathy.

Young et al reported complications related to procedures undertaken on 1050 patients aged 17 – 89 years.[10] All were administered iodixanol, approximately 3 mL/kg body weight. The most common complications were haematoma/bruising (11%) and local pain (8.6%). One patient died of a ruptured aortic aneurism 2 days after the procedure; the death was considered unrelated to the investigation. Eight cases of allergy to the contrast agent were reported. One patient suffered anaphylaxis. Two patients undergoing cerebral studies reported a transient ischaemic attack and one a cerebrovascular accident.

Post-marketing experience

Since the launch in September 1992, approximately 62,648,281 million vials were calculated to have been sold world wide. The sponsor assumes use of 1 vial per person on average. The safety database was searched for the age groups from 0 to 18 years, or the equivalent in months, weeks or days. In addition the terms newborn and child were added to the search.

A total of 94 reports were retrieved including 106 adverse reactions. Twenty-seven reports including 32 reactions were serious. 65 reports including 71 reactions were non-serious and 2 reports including 3 reactions were unspecified with regard to seriousness.

Six reports concerned a fatal outcome - 3 cardiovascular, 1 infectious, 1 renal and 1 respiratory. Only in the renal case was Visipaque considered to have contributed to the outcome. Of the 21 non-fatal serious reactions, 14 were considered to have a causal relationship to Visipaque, 4 were considered to be unrelated, 2 had uncertain relationship and 1 had unknown relationship.

In summary,

- A 27 month old girl experienced the SAE of renal failure and hypersensitivity considered related to VIS-320 administered at the time of cardiac catheterisation, and immunosuppression ad fever considered possibly related.

[9] Wang CL, Cohan RH et al. Frequency, management and outcome of extravasation of nonionic iodinated contrast medium in 69 657 intravenous injections. Radiology 2007; 243: 80 – 87.

[10] Young N, Chi, K-K et al. Complications with outpatient angiography and interventional procedures. Cardiovasc Intrevent Radiol 2002; 25: 123 – 126.

- A five year old boy experienced acute renal failure considered related to Visipaque of unknown concentration following cardiac catheterisation.
- A two year old girl developed renal failure to which VIS-320 may have contributed following cardiac catheterisation.
- A16 year old administered VIS-270 for head CT experienced dyspnoea, a know/listed reaction but causality not stated in the report.

Clinical Summary and Conclusions

Pharmacokinetics

The Phase I, open label, multicentre pharmacokinetic study including 43 children from newborn to 12 years of age who received intra-arterial iodixanol 320 in all but two instances when the intravenous route was used. The mean dose was 1.49 g I/kg and mean volume was 4.67 mL/kg.

Pharmacokinetic results were consistent with an increased rate of excretion with increasing postnatal age and concurrent increase in renal maturity. The one patient with renal failure had a markedly protracted half life. The 8 infants less than 2 months of age had significantly lower mean k_{el} results than older children and children older than 6 months had similar mean k_{el} results to adults. As relatively higher doses are often required for the youngest children, safety of the contrast medium in the very young must be considered a matter of special interest.

For these investigations, assessment of efficacy was not an objective, however in terms of the quality of visualisation the results were reported to be excellent or good for all patients.

The study was not powered and the sample number not calculated to assess safety. There was one death – a child with hypoplastic left heart, sepsis and renal failure, considered unrelated to the study drug. The most common adverse event was vomiting (5 of 43 subjects); nausea was reported for 3/43, however many of the patients would have been too young to report this subjective AE. Injection site pain was reported for 2 patients, one of whom is recorded as being less than 12 months of age. Injection related distress was not noted. In the supplied table, injection site pain was considered unrelated to study drug

Randomised, Controlled Trials

There were ten randomised controlled trials included in the submission, two each for urography, CT of the head, CT of the body, angiography and gastrointestinal studies.

The studies utilising intravenous or intra-arterial administration of the study drug included 145 patients who received VIS-270, 152 who received VIS-320 and 150 administered iohexol. The six intravenous trials compared safety and efficacy of use of iodixanol 270 mg I/mL or iodixanol 320 mg I/mL with iohexol 300 mg I/mL. The angiocardiography studies compared safety and efficacy iodixanol 320 mg I/mL with iohexol 350 mg I/mL.

The basic design and execution of the studies utilising parenteral administration of contrast agent was considered to be good and a testament to the fact that good quality paediatric studies can be done despite the technical difficulties and ethical considerations. However, there were perceived problems with three of the studies[11] in which consent for one or more patients was not properly obtained. Obtaining consent in accordance with an IRB approved

[11] Study Report 1967 - Computed Tomograph Scanning of Body; DXV036 Angiocardiography – Phase III; Study Report 1968 – Angiocardiography

protocol requirement is considered the bedrock of ethical human research. Patients without such consent should be excluded.

Not all studies in which it was planned had laboratory parameters measured, and in those studies in which they were undertaken, not all patients had laboratory results available. The difficulties entailed in obtaining samples are acknowledged. Two studies had changes made to age stratification after the commencement of the trials.

The main efficacy outcome, the quality of visualisation for studies utilising parenteral administration of study drug was generally reported as excellent or good for all types of contrast enhanced investigation. The contributions of the contrast agent to the ability to make a radiographic diagnosis and the ability to rule in or rule out presumptive diagnoses were consistently highly rated by the investigators.

Statistical analyses relevant to the results appeared to have been decided post-hoc. However it appeared plain that the results for each formulation were not very different and if a difference exists, large numbers of study participants would be needed for statistical proof.

For gastrointestinal use efficacy and safety of Visipaque 150 mg I/mL and 320 mg I/mL were compared to Omnipaque 140 mg I/mL and 300 mg I/mL in one study and iodixanol 150 mg I/ml and iodixanol 270 mg I/mL were compared to iohexol 140 mg I/mL and 300 mg I/mL in the other study. However, participant disposition was so scantily described in the submission that it was difficult to ascertain how many patients received each of the formulations. The evaluator calculated 111 in the iodixanol treated groups and 133 in the iohexol groups but the numbers administered high and low dose could not be determined.

In GI Study DXC060, the primary objective of the study was not stated as such but was implied by the description of the main endpoint. Stratification appeared somewhat arbitrary and randomisation procedure was not followed in one centre. The analysis of results obtained for the main endpoint excluded patients for reason which did not appear to be pre-specified in the protocol, that is, the concentration of fruit juice given with the test products. This omission of patients was considered to result in the possibility to bias.

Study CXC064 also lacked detail about the numbers treated with each formulation. In this study rectal administration was not allowed following a protocol amendment. The results of this study appeared highly influenced by centre

The primary efficacy result for these studies was a Visual Analogue Scale score. The 95% CIs for the differences noted in both studies included zero which would suggest that no statistical difference was shown to have existed between results for the two formulations.

Excluding the results of the two pilot studies and the pharmacokinetic study, safety results for the two urography studies, the four CT studies, the two angiocardiography studies and the two studies for gastrointestinal use were collated by the sponsor. Apart from tables on the overall design of the studies, the overall demographic characteristics and the doses, the summary was considered deficient in that the AEs were summarised for all participants rather than for groups treated with specific formulations. AEs were not described and no attempt to determine the most common AEs and those considered related to study drug could be discerned. For this reason and because of time constraints, the safety findings of the studies are described separately in this report and briefly summarised in the overview according to the evaluator's understanding below.

There were four deaths included in Report 1968 – angiocardiography: two were considered unrelated and two were considered unlikely to be related - both these reports were of cardiogenic shock, and one also included disseminated intravascular coagulation and acute

renal failure. One patient administered VIS-320 was reported to experience the serious adverse event of atrial flutter but this was not attributed to the contrast agent. Decreases in lymphocyte counts were noted by the evaluator but were not commented upon in the investigator's report.

Injection associated discomfort was reported in each of the studies involving injection of contrast agent; the majority of reports citing cold, heat or pain. The relevant denominator was not universally reported, and hence it was not possible to collate these results in any meaningful way. Injection associated distress was not universally reported as having occurred, and it would appear the investigators in different centres may have had differing sensitivity to the presence of signs of distress. Most of the study investigators reported few if any episodes of distress while investigators involved in Study Report 1968 reported 22 episodes of injection related distress.

Nausea was reported for one or two patients in many of the studies but was often considered of uncertain relationship. Not all patients would have been able to report this symptom.

The following AEs were considered by the investigator's to be study drug related. Each dot point relates to one patient.

VIS-320:

- Itching throat
- Periorbital oedema.
- Increase in creatinine.
- Nausea x 2, itching x 2 , increased sweating x 2 and vomiting.
- Vertigo judged to be *procedure* related

VIS-270

- Tiredness, nausea x2; smell perversion and metallic taste in mouth.
- Exanthema;
- Bad taste in mouth

Iohexol

- Taste perversion
- Nausea, vomiting
- Increase in AST/ALT

The probable cause for most arrhythmias in the angiocardiography studies was not reported.

The adverse events reported in the gastrointestinal studies were largely reported as being of uncertain relationship to the study drugs. In study DXC060, diarrhoea was the most commonly reported AE both overall and considered related to study drug. One patient in this study experienced, rash, itch and fever considered related to VIS-320 administration. More patients in this study exposed to iohexol experienced diarrhoea than patients exposed to VIS-320, however the study was not planned or powered to show a statistically significant difference.

In the gastrointestinal study DXC064 the only AE considered study drug related was aspiration reported for one patient in the iohexol group. All other AEs were reported as either not related or of uncertain relationship. Again, the most common AE was diarrhoea and only for one patient was it reported to have predated the investigation. The reason for discounting the relationship to study drug was not stated.

In the post-marketing report summary, three children undergoing cardiac catheterisation experienced renal failure in which Visipaque was implicated and one child developed dyspnoea, a listed reaction but with causality not stated in the report.

The literature search did not add significantly to the information discussed above. Two of the articles related to studies submitted for evaluation.

Conclusion and Recommendation

The efficacy of the two formulations of Visipaque is considered to have been demonstrated when used for cardioangiography, urography, cranial CT and CT of the body, and gastrointestinal studies in patients from birth to 17 years of age, and from weight above 2000 - 2500 grams.

From the safety aspect, few adverse events were attributed to the study contrast agent formulations. Many of the patients involved in the study had indications for those studies which would complicate assessment of the relationship of study drug to reported adverse events.

Risk/Benefit

The risks involved in use of the contrast agent in children, particularly in very young children include:

- The volume of injected fluid which tends to be greater per kilogram in the youngest patients who may be least tolerant of fluid loading
- The reduced elimination rate of the products in the neonates and in young infants and the higher doses per kilogram often required in the youngest patients particularly those undergoing angiocardiography
- The adverse event profile known to exist in the adult population
- The inability of very young patients to report subjectively perceived symptoms leading to under-reporting of these events
- The possible added safety risk of sedation or anaesthesia
- The possibility that use of contrast may hide lesions which do not enhance
- The procedure of injection of the contrast medium may be complicated. Thin needles and catheters are preferred and high viscosity may cause unwanted prolonged injection time. Preheating the contrast medium to 37 °C for all procedures with catheter applications may reduce the problem of viscosity.
- The concentration of iodine is expressed in mg per mL in the description of the product, but in the dosage and administration section, the dose is expressed in grams iodine. This is the source of potential problems in the paediatric setting where mistakes in calculation of dosages occur not infrequently when information includes differing denominations.

The benefits include the demonstrated efficacy in terms of contrast enhanced visualisation and added diagnostic certainly in situations where non-invasive diagnostic techniques are unsuitable or inadequate.

Recommendation

The balance of risk and benefit is considered to lie on the side of benefit for those patients for whom other, less invasive modalities of investigation are considered inappropriate. The requested extension of indication is recommended.

V. Pharmacovigilance Findings

Risk Management Plan

The TGA's Office of Medicines Safety Monitoring (OMSM) reviewed the sponsor's submitted Risk Management Plan (RMP), which proposed the following in regard to the use of Visipaque in the paediatric population:

- Routine pharmacovigilance activities: the processing and submission of individual case safety reports (adverse drug reaction reports), the production of periodic safety update reports (PSURs), safety monitoring activities and activities of the EU Qualified Person for Pharmacovigilance were described.
- The sponsor's safety specification for Visipaque in subjects below 18 years of age did not indicate an identified or a potential safety concern or any lacking information. Therefore, routine pharmacovigilance activities were considered sufficient by the sponsor.
- An assessment of the requirement to provide a risk minimisation plan: six potential safety issues were regarded to be either theoretical (for example, hypothyroidism in newborn following exposure *in utero* or potential adverse effects related to the viscosity of Visipaque), related to the underlying condition or the interventional procedure, or related to hypersensitivity. Therefore the sponsor concluded that use of Visipaque in children does not constitute an identified or a potential safety concern, and there is no information lacking. Consequently routine risk minimisation activities were considered sufficient.
- Proposed risk minimisation activities: preventable risks were adequately addressed in the prescribing information.

The OMSM considered it highly unusual that there were no important identified or potential risks or that there was no important missing information associated with the use of a medicine. These classifications do not necessarily imply that additional pharmacovigilance or additional risk minimisation activities are warranted, particularly in the context of significant post-marketing experience.

Based upon the sponsor's evaluation and the proposed PI, the TGA considered that the safety specifications should be amended as follows:

Important identified risks:

- Hypersensitivity

Important potential risks:

- Congenital hypothyroidism following iodide exposure in utero
- Adverse reactions related to relatively high doses and age dependent renal immaturity
- Adverse events in connection with cardiac or other major surgery
- Aspiration following oral use
- Physicochemical properties, for example, viscosity

Important missing information:

- Pregnant and lactating females
- Paediatric off-label use

There would appear to be significant international post-marketing experience in the use of iodixanol in adults and children. In this context the submitted RMP, which only proposes the application of routine pharmacovigilance and routine risk minimisation activities in regard to the use of iodixanol in children, is acceptable if amendments to the safety specifications as suggested by the TGA are adopted.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There is no requirement for a quality evaluation in an application of this type.

Nonclinical

No new nonclinical studies were submitted. Reports of reproductive toxicity studies and a single dose study in juvenile rats had previously been submitted. The single dose study in juvenile rats indicated that iodixanol is more toxic in juveniles than adults, probably as a result of immature renal function in juveniles and/or faster injection speed. The peri/postnatal study showed only minor findings but is of little value as there was no pup exposure data. The available nonclinical data are insufficient to support paediatric use of iodixanol. The sponsor has justified the lack of new nonclinical studies on the grounds that safety data from adults represent the most relevant information, and safety and efficacy have been established in the human paediatric population with registration in many countries.

Clinical

Pharmacokinetics

Study Report 2493 is a Phase I open-label, multicentre, pharmacokinetic and safety trial in paediatric patients, newborn to 12 years of age. Study objectives were to determine the pharmacokinetic profile of iodixanol injection 320 mg I/mL (VIS-320) in plasma (terminal elimination rate constant (k_{el}) was primary endpoint) and to assess the safety of VIS-320. Patients were aged from 36 weeks gestation to 12 years who were referred for iodinated, contrast –enhanced intravascular diagnostic procedures including, but not limited to angiocardiography, CT scanning of the head and CT scanning of the body. Dosing was performed according to each trial centre's standard procedures. A total of 43 patients were enrolled into five groups. All patients completed the trial.

Subject numbers were: newborn to < 2 months; 8 patients, 2 to < 6 months; 9 patients, 6 to < 12 months; 10 patients, 1 year to < 3 years; 8 patients, 3 to 12 years; 8 patients.

The mean dose was 1.49 g I/kg and mean volume was 4.67 mL/kg. The mean k_{el} was significantly lower in the newborn to < 2 months age group than in any of the three oldest age groups; the 2 to < 6 month age group mean k_{el} was intermediate between the youngest and older patients. A model was used to calculated $t_{½}$. In infants < 2 years of age, the $t_{½}$ of iodixanol was approximately 4.1 hours. For children 2 – 6 months of age the $t_{½}$ was approximately 2.8 hours. In children > 6 months of age but < 12 years, the $t_{½}$ was 2.3 hours, approximating that of adult. The quality of visualisation or enhancement was considered adequate for diagnosis in all 43 patients and was considered excellent for 41 (95%) and good for 2 (5%).

Efficacy

Ten paediatric clinical studies compared safety and efficacy of iodixanol with iohexol. These Phase III studies were randomised, double-blind and active comparator controlled.

The studies of excretory urography, cranial computed tomography and computed tomography of the body assessed iodixanol 320 mg (VIS-320) and iodixanol 270 mg I/mL (VIS – 270) compared to iohexol 300 mg I/mL. In each study 75 patients were planned for enrolment to be randomly allocated to three groups of 25 patients. Two angiocardiography studies with similar design were included in which patients were assigned to receive either VIS320 or

iohexol 350 mg I/mL. In addition two gastrointestinal contrast studies were included in which patients were assigned to receive test agent Visipaque 150 mg I/mL, 320 mg I/mL or 270 mg I/mL or comparator Omnipaque 140 mg I/mL or 300 mg I/mL.

Efficacy was assessed by investigator and scored for overall diagnostic information, ability to obtain radiographic diagnosis and diagnostic utility.

The main efficacy outcome - quality of visualization for studies utilising parenteral administration of study drug - was generally reported as excellent or good for all types of contrast enhanced investigation. Investigators rated highly the contribution of contrast to obtain a radiological diagnosis and the ability to rule in or out presumptive diagnoses.

For gastrointestinal studies visualisation scores were not significantly different between iodixanol and iohexol groups at similar concentrations, although patient disposition was difficult to ascertain and reasons for exclusion of patients from analysis of primary endpoint did not appear to have been prespecified in DXC060.

Safety

A total of 901 infants and children in controlled studies, of whom 321 were younger than 12 months of age. In total 534 patients received iodixanol and 376 received iohexol.

In Phase III clinical studies AE were monitored for 1 day after parenteral administration and for 2 days after gastrointestinal use. Vital signs were monitored in all studies. Laboratory parameters were measured in parenteral studies except for excretory urography. ECGs and haemodynamics were recorded for the 2 angiocardiography studies. Occurrence of bronchial aspiration and taste acceptance were monitored in the gastrointestinal studies.

Injection associated discomfort was reported in each of the parenteral studies but with few reports of severe discomfort or distress, except in Study 1968 in which there were 22 episodes of injection related distress. Four deaths were reported in Study 1968. Two were considered not study drug related and two were considered unlikely related. These were both reports of cardiogenic shock, with one also involving DIC and acute renal failure. A serious event of atrial flutter was also reported in this study considered unrelated to study drug.

In gastrointestinal study DXC064 aspiration was a drug related event in 1 patient. In this study diarrhoea was reported in 16 patients in the iodixanol group and 21 patients in the iohexol group.

The literature search did not add significant additional safety information.

The Post-Marketing Report prepared in 2009 identified only listed serious drug related reports, with 3 reports of renal failure in children.

Clinical Evaluator Conclusions

The evaluator considered that efficacy of iodixanol 270 mg I/mL and 320 mg I/mL had been demonstrated in cardioangiography, urography, CT-enhancement of the head and body and studies of the upper gastrointestinal tract, in patients from birth to 17 years, and weight above 2000-2500 grams.

Few adverse events were attributed to study contrast agent formulations.

The evaluator recommended registration of the extension of indications as benefit/risk ratio is positive for those patients for whom less invasive modalities of investigation are inappropriate.

Risk Management Plan

The submitted Risk Management Plan has been reviewed by the OMSM. The sponsor accepted some recommended amendments to safety specifications. Routine pharmacovigilance and routine risk management activities have been proposed in regard to the use of iodixanol in children, and this has been accepted by OMSM.

Risk-Benefit Analysis

The nonclinical evaluation concluded that nonclinical data are insufficient to support paediatric use of iodixanol. The Delegate accepted that the submitted paediatric clinical studies and post-marketing experience in countries that the product is approved for paediatric use (including Sweden, UK and USA) adequately establish the safety and efficacy of iodixanol in the paediatric population.

The Delegate proposed to register iodixanol (Visipaque) 270 mg I/mL and 320 mg I/mL solution for injection for an extension of indications to include cardiography, urography, CT-enhancement and studies of the upper gastrointestinal tract.

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended the following extension of indications:

Visipaque is indicated in children for:

- *cardioangiography, urography, CT-enhancement and studies of the upper gastrointestinal tract.*

In making this recommendation the ACPM agreed with the Delegate that the evidence of the safety and efficacy of the formulation and the dosage regimen is sufficient to support the extension of the indication to include this population group. The ACPM supported the changes to the PI noting that they have been adopted by the sponsor. The ACPM noted the advice of its Pharmaceutical Subcommittee (PSC) that the population based pharmacokinetics have not been assessed by a specialist in this area.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Visipaque containing iodixanol 550mg/mL and 652mg/mL injections for the extended indication and for use in accordance with the following approved indications:

This medicinal product is for diagnostic use only.

Visipaque is indicated in adult patients for angiocardiography, peripheral arteriography, visceral arteriography, cerebral arteriography, contrast-enhanced computed tomography of the head and body, excretory urography and venography. In arteriography, Visipaque may be used for both conventional radiography and digital subtraction angiography (DSA).

In children, Visipaque is indicated for cardioangiography, urography, CT enhancement and studies of the upper gastrointestinal tract.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

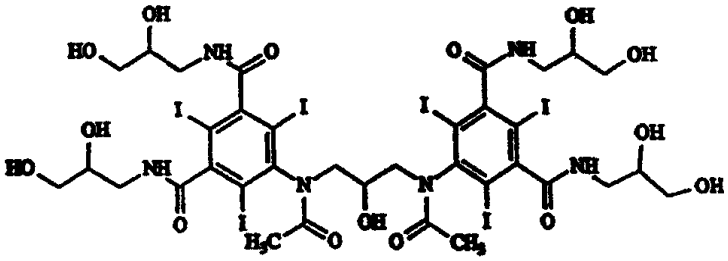
VISIPAQUE® (IODIXANOL) INJECTION

NAME OF THE MEDICINE

VISIPAQUE 270 mg I/ml and 320 mg I/ml Solution for Injection.

DESCRIPTION

VISIPAQUE (Iodixanol) Injection, 5,5-[(2-hydroxy-1,3 propanediyl)bis(acetylimino)] bis(N,N'-bis(2-3-dihydroxypropyl)-2,4,8-triiodo-1,3-benzenedicarboxamide], is a dimeric, nonionic, water-soluble, radiographic contrast medium with a molecular weight of 1550.20 (iodine content 49.1%). It is administered by intravascular injection. VISIPAQUE ($C_{35}H_{44}I_6N_6O_{15}$) has the following chemical structure:



Active ingredient	Strength	Content per. ml.
Iodixanol (INN)	270 mg I/ml	550 mg equiv. 270 mg I
Iodixanol (INN)	320 mg I/ml	652 mg equiv. 320 mg I

The osmolality, viscosity and density values of Visipaque are as follows:

Concentration	Osmolality* mOsm/kg H_2O 37°C	Viscosity (mPa·s)		Density (g/ml)	
		20°C	37°C	20°C	37°C
270 mg I/ml	290	11.3	5.8	1.369	1.314
320 mg I/ml	290	25.4	11.4	1.356	1.303

* Method: vapour-pressure osmometry

For a full list of excipients, see section Presentation and storage conditions.

Solution for injection. VISIPAQUE is supplied ready to use as clear, colourless to pale yellow aqueous solutions.

All solutions are terminally sterilised by autoclaving and contain no preservatives.

Iodixanol is a non-ionic, dimeric, hexaiodinated, water-soluble X-ray contrast medium.

Pure aqueous solutions of iodixanol in all clinical relevant concentrations have a lower osmolality than whole blood and the corresponding strengths of the non-ionic monomeric contrast media. VISIPAQUE is made isotonic with normal body fluids by addition of electrolytes.

PHARMACOLOGY

Pharmacodynamic properties

The organically bound iodine attenuates radiation in the blood vessels/tissues when it is injected.

For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iodixanol 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.

In a study involving 129 diabetic patients with serum creatinine levels of 1.5 – 3.5 mg/dl, use of VISIPAQUE resulted in 3% of patients experiencing a rise in creatinine of ≥0.5 mg/dl and no patients with a rise of ≥1.0 mg/dl. The peak increase in the serum creatinine concentration within three days after the administration of VISIPAQUE was 0.13 mg per dl (11.2 µmol per litre). A transient increase in tubular enzyme excretion was observed after contrast media injection. However, lower or similar effects on the release of enzymes (alkaline phosphatase and N-acetyl-ß-glucosaminidase) from the proximal tubular cells were observed for VISIPAQUE in comparison to ioxaglate.

Cardiovascular parameters such as LVEDP, LVSP, heart rate and QT-time as well as femoral blood flow were less influenced after VISIPAQUE than after other contrast media, where measured.

Pharmacokinetic properties

Iodixanol is rapidly distributed in the body with a mean distribution half-life of approximately 21 minutes. The apparent volume of distribution is of the same magnitude as the extracellular fluid (0.26 l/kg b.w.), indicating that iodixanol is distributed in the extra-cellular volume only.

VISIPAQUE displayed no protein binding in vitro (less than 2% detectable limit) at a 1.2 mg I/ml concentration in human plasma. No significant metabolism, deiodination or biotransformation has been detected in animals.

The mean elimination half-life is approximately 2 hours. Iodixanol is excreted mainly through the kidneys by glomerular filtration. Approximately 80% of the administered dose is recovered unmetabolized in the urine within 4 hours and 97% within 24 hours after intravenous injection in healthy volunteers. Only about 1.2% of the injected dose is excreted in faeces within 72 hours. The maximum urinary concentration appears within approximately 1 hour after injection.

No dose dependent kinetics have been observed in the recommended dose range.

Paeditric Pharmacokinetics

Forty three (43) paediatric patients <12 years old, with renal function that is normal for their age, received multiple intra-arterial administrations of VISIPAQUE Injection in doses of 0.32 to 3.2 gI/kg body weight. The elimination half-lives for these patients are derived from the mean terminal elimination rate constants (K_{el}): 0.185/hr (newborn to 2 months old), 0.256/hr (2 to <6 months old), 0.299/hr (6 months to <1 year), 0.322/hr (1 to <2 years), and 0.307/hr (2 to <12 years old). The adult mean terminal elimination rate constant is 0.336/hr.

The actual VISIPAQUE clearance and volume of distribution in pediatric patients were not determined. Pharmacodynamic dose adjustments to account for differences in elimination half-life in pediatric patients under 6 months of age have not been studied.

CLINICAL TRIALS

The safety and efficacy of VISIPAQUE has been established in the paediatric population for arterial studies, for intravenous procedures and gastrointestinal use. Use of VISIPAQUE in these age groups is supported by evidence from adequate and well controlled studies of VISIPAQUE in adults and additional safety data obtained in paediatric studies.

The clinical development of VISIPAQUE comprised: one pharmacokinetic study in 43 subjects and another ten clinical studies to demonstrate efficacy and safety of VISIPAQUE.

Six studies for intavenous use (two urography studies, four CT studies), two studies for intra-arterial use (two cardioangiography studies) and two studies for gastrointestinal use. In two of these studies there was a pilot part including 3 and 10 patients, respectively. Otherwise the studies were phase III, randomized, double-blind,parallel-group comparison between iodixanol (VISIPAQUE) and iohexol (Omnipaque).

A total of 638 infants and children were included in the clinical trials. They aged between birth and up to 17 years, 225 of them were younger than 24 months. Of these 403 received iodixanol and 235 patients received iohexol. The patients were equally distributed concerning age, sex and body weight in all study groups. Neonates were not enrolled in these studies with no child included with body weight <2Kg.

All the intravascular studies (intravenous and intra-arterial) showed that iodixanol was efficacious. No significant differences were detected between the iodixanol and iohexol groups. VISIPAQUE also gave appropriate contrast in all areas of the gastrointestinal tract and was found to be well suited for gastrointestinal examinations in the paediatric population. VISIPAQUE can also be used safely in the paediatric population.

INDICATIONS

This medicinal product is for diagnostic use only.

VISIPAQUE is indicated, in adult patients, for angiocardiography, peripheral arteriography, visceral arteriography, cerebral arteriography, contrast-enhanced computed tomography of the head and body, excretory urography and venography. In arteriography, VISIPAQUE may be used for both conventional radiography and digital subtraction angiography (DSA).

In children, VISIPAQUE is indicated for cardioangiography, urography, CT-enhancement and studies of the upper gastrointestinal tract.

CONTRAINDICATIONS

Hypersensitivity to the active substance or iodine or hypersensitivity to any of the excipients.
History of serious hypersensitivity reaction to VISIPAQUE.
Manifest thyrotoxicosis.

PRECAUTIONS

Precautions in general

The risk of serious reactions in connection with use of VISIPAQUE is regarded as minor. However, iodinated contrast media may provoke anaphylactoid reactions or other manifestations of hypersensitivity. 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.

As with other iodinated contrast agents, the use of VISIPAQUE injection contrast enhancement may obscure some lesions which are seen on previously unenhanced CT scans.

In patients with normal blood-brain barriers and renal failure, iodinated contrast agents have been associated with blood-brain barrier disruption and accumulation of contrast in the brain.

Enhancement of the inferior vermis following contrast agent administration has resulted in false-positive diagnosis.

Hydration
Patients should be well hydrated prior to, and following, administration of any contrast medium, including VISIPAQUE, in order to prevent from acute renal failure. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction and elderly patients. Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with pre-existing renal insufficiency, diabetes or advanced vascular disease. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualisation in normal patients.

To avoid contrast induced nephropathy, the following should be considered:

- Identification of high risk patients
- Ensuring adequate hydration. The patient should be hydrated (e.g. at least 100 mL per hour of soft drinks or intravenous saline up to 24 hours after contrast medium administration. In warm areas more fluid should be given).
- 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.
- Monitor renal function (serum creatinine), serum lactic acid and pH of blood.
- Look for symptoms of lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnea, lethargy, diarrhoea and thirst). Blood test results indicative of lactic acidosis: pH<7.25 and lactic acid > 5 mmol.

Paediatrics
In the paediatric population, prolonged fasting and the administration of a laxative before VISIPAQUE injection are to be avoided.

Adequate hydration should be ensured; infants and especially neonates are susceptible to electrolyte disturbance and haemodynamic changes.

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

Patients with thyrotoxicosis or hyperthyroidism
Iodinated contrast media should not be administered to patients with thyrotoxicosis (see Contra-indications).
Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goiter may be at risk of developing hyperthyroidism following injection of iodinated contrast media.

Patients with history of allergic reactions
A positive history of allergy, asthma, or untoward reactions to iodinated contrast media indicates a need for special caution. Premedication with corticosteroids or histamine H1 and H2 antagonists might be considered in these cases. Recent reports of the use of iodinated contrast agents indicate that such pretreatment does not prevent serious life-threatening reactions but may reduce both their incidence and severity.

Patients with multiple myeloma
Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemias, particularly in those with the therapeutically resistant anuria. Although neither the contrast agent nor dehydration have been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication; however, they require special precautions. Preparatory dehydration of these patients is not recommended since it may predispose the patient to precipitation of the myeloma protein in the renal tubules. The presence of myeloma should be considered before instituting intravascular administration of contrast agents.

Patients with phaeochromocytoma
Administration of radiopaque materials to patients known to have, or suspected of having, phaeochromocytoma 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.

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

Patients with a history of seizures
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.

Patients with serious cardiac disease and pulmonary hypertension
Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias.

Diabetic patients treated with metformin
To prevent lactic acidosis, serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium.

- Normal serum creatinine/renal function: administration of metformin should be stopped at the time of administration of the contrast medium and not resumed for 48 hours or until renal function/serum creatinine is normal.

- Abnormal serum creatinine/renal function: metformin should be stopped and the contrast examination delayed for 48 hours. Metformin should only be restarted if renal function (serum creatinine) is unchanged.
- 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.

Patients with pre-existing renal impairment
A benefit to risk assessment should be made before use of an iodinated contrast medium in patients with pre-existing renal impairment (serum creatinine > 1.5 mg/dL).

Iso-osmolar or low-osmolar contrast media should always be used in these patients.

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 media induced nephrotoxicity. If clinically indicated, haemodialysis is an effective method for eliminating iodinated contrast medium from the body. Correlating the time of contrast medium to the dialysis schedule is unnecessary, because there is no evidence that haemodialysis protects patients with impaired renal function from contrast media 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.

Patients on haemodialysis may receive contrast media for radiological procedures.

Complications of catheterisation
In angiographic procedures, the possibility of dislodging plaques, rupturing aneurisms, or damaging or perforating the vessel wall should be borne in mind during catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Non-ionic contrast media have less effect on the coagulation system in vitro, compared to ionic contrast media. For these reasons, meticulous intravascular administration technique is necessary, particularly during angiographic procedures. Close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinised saline solutions, and minimising the length of the procedure may minimise thromboembolic events. Numerous factors, including catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

No safety data have been submitted regarding the following:

- Pregnant and lactating women
- Patients with unstable medical conditions
- Severe pulmonary hypertension
- Uncontrolled arrhythmias

- Decompensated congestive cardiac failure
- Aortic stenosis
- Acute intracranial haemorrhage
- Recent head trauma
- Patients who have had a myocardial infarction in the previous three days

Extravasation
It is likely that extravasation of VISIPAQUE, due to its isotonicity, gives rise to less local pain and extravascular oedema than hyperosmolar contrast media. In case of extravasation, 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, experience shows that hypersensitivity reactions, mostly mild to moderate skin reactions, may appear up to several hours or days post injection.

Special precautions by indication

Cardioangiography: Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the risk. The inherent risks of angiocardiography in patients with chronic obstructive pulmonary disease must be weighed against the necessity for performing this procedure.
During left ventriculography and coronary arteriography, vital signs and the ECG should be monitored routinely throughout the procedure. 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.
Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds, because of the haemodynamic changes that may occur after injection into the right heart outflow tract.

Peripheral Arteriography: Pulsation should be present in the artery to be injected. In thromboangiitis obliterans or ascending infection associated with severe ischaemia, arteriography should be performed only if the benefits clearly outweigh the risks.

Visceral Arteriography/Selective visceral i.a. DSA: In thromboangiitis obliterans or ascending infection associated with severe ischaemia, arteriography should be performed only if the benefits clearly outweigh the risks.

Cerebral Arteriography: Cerebral arteriography should be undertaken with extreme care, especially in elderly patients, patients in poor clinical condition, or patients with advanced arteriosclerosis, severe arterial hypertension, cardiac decompensation or recent cerebral embolism or thrombosis.

Since VISIPAQUE is given by rapid injection, the patient should be monitored for possible untoward reactions. In cerebral arteriography, patients should be appropriately prepared consistent with existing or suspected disease states.

In patients with cerebral haemorrhage, a rare association between contrast administration and clinical deterioration, including severe headache and death, has been reported. Therefore, administration of intra-arterial iodinated contrast media in these patients should be undertaken with caution.

Venography: In thromboangiitis obliterans or ascending infection associated with severe ischaemia, venography should be performed only if the benefits clearly outweigh the risks.

Excretory Urography: Urography should be performed with caution in patients with impaired renal function, patients with combined renal and hepatic disease, and patients with diabetic nephropathy.

Use in pregnancy (Category B1).
Since, wherever possible, radiation exposure should be avoided during pregnancy, the benefits of any X-ray examination, with or without contrast media, should be carefully weighed against the possible risk. The product should not be used in pregnancy unless benefit outweighs risk and it is considered essential by the physician.

Reproduction studies have been performed in rats and rabbits at doses up to 2 gI/kg/day and have revealed no evidence of harm to the foetus due to VISIPAQUE. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the drug should be used during pregnancy only if clearly needed.

Labour and delivery
It is not known whether the use of contrast agents during labour or delivery has immediate or delayed effects on the foetus, prolongs the duration of labour or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Use in lactation
Occurrence of serious adverse reactions has not been established in nursing infants.

The amount of contrast medium excreted in human milk appears to be low. Nursing may be continued normally when iodinated contrast media are given to the mother.

Effects on the ability to drive and use machines
None known.

Effects on Fertility
VISIPAQUE did not affect male or female fertility in rats at IV doses up to 2 gI/kg/day.

Carcinogenicity
No long-term animal studies have been performed to evaluate the carcinogenic potential of VISIPAQUE.

Genotoxicity
VISIPAQUE did not induce gene mutation in bacteria or Chinese hamster ovary (CHO) cells *in vitro.* It was not clastogenic in CHO cells *in vitro* or in mice *in vivo.*

Interaction with other medicines
Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking biguanides/metformin (see Special warnings and special precautions for use).

Patients treated with interleukin-2 less than two weeks previous to an iodinated contrast medium injection have been associated with an increased risk for delayed reactions (flu-like symptoms or skin reactions).

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.

General anaesthesia may be indicated in the performance of some procedures in selected patients. However, a higher incidence of adverse reactions following administration of contrast agents has been reported in anaesthetised patients. This may be attributable either to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anaesthesia, which can reduce cardiac output and increase the duration of exposure to a contrast agent.

Patients using beta blockers may present with atypical symptoms of anaphylaxis which may be misinterpreted as a vagal reaction (see Undesirable effects).

Addition of an inotropic agent to contrast agents may produce a paradoxical depressant response, which can be deleterious to the ischaemic myocardium.

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs. Therefore, other pharmaceuticals should not be mixed with contrast agents, including VISIPAQUE, in the same syringe.

Effects on Laboratory Tests
Protein-bound iodine (PBI) and total serum organic iodine: transient increases of both tests following urography have been noticed. The results of PBI and radioactive iodine uptake studies which depend on iodine estimations will not accurately reflect thyroid function for up to 16 days following administration of iodinated urographic media. However, thyroid function tests not depending on iodine estimations, such as T_3, resin uptake or free thyroxine assays, are not affected.

VISIPAQUE interferes with Multistix measurements of specific gravity and produces a false-positive result for protein in the urine *via* Multistix. However, the Coomassie blue method has been shown to give accurate results for the measurement of urine protein in the presence of VISIPAQUE.

ADVERSE EFFECTS
Below are listed possible side effects in relation with radiographic procedures which include the use of VISIPAQUE.

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

Hypersensitivity reactions usually present as respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus, skin reaction, angioneurotic oedema, hypotension, fever, 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 hypersensitivity which may be misinterpreted as a vagal reaction.

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

An undesirable effect is said to be:

• very common 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 studies, comprising more than 48,000 patients.

Adults Intravascular use (Intra-arterial and Intravenous use):

MedDRA System Organ Class	**Adverse Drug Reaction (ADR)**	**Frequency**
Immune system disorders	Hypersensitivity	Uncommon
	Anaphylactoid reaction	Not known
	Anaphylactoid shock	Not known
	severe pustular or bullous skin reactions	Not known
Psychiatric disorders	Confusional state	Not known
Nervous system disorders	Headache	Uncommon
	Dizziness	Rare
	Sensory disturbance	Very rare
	Motor dysfunction	Not known
	Convulsion	Not known
	Disturbance in consciousness	Not known
Eye disorders	Blindness transient	Very rare
Cardiac disorders	Arrhythmia	Rare
	Ventricular hypokinesia	Not known
	Myocardial ischaemia	Not known
Vascular disorders	Hypotension	Rare
	Hypertension	Very rare
	Ischaemia	Very rare
	Arterial spasm	Not known
	Thrombosis	Not known
	Thrombophlebitis	Not known
Respiratory, thoracic and mediastineal disorders	Cough	Rare
	Dyspnoea	Very rare
	Non-cardiogenic pulmonary oedema	Not known
Gastrointestinal disorders	Nausea	Uncommon
	Vomiting	Uncommon
	Abdominal pain/discomfort	Very rare
Musculoskeletal, connective tissue and bone disorders	Arthralgia	Not known
Renal and urinary disorders	Acute renal failure	Very rare
General disorders and administration site conditions	Feeling hot	Uncommon
	Pain	Rare
	Pyrexia	Rare
	Feeling cold	Very rare
	Asthenic conditions (e.g., malaise, fatigue)	Very rare
Injury and poisoning	Iodism	Not known

Paediatrics:

In general the type of adverse events reported are similar to those of adults. Although the frequency of events appears to be comparable, the frequency cannot be confirmed because of the different ability of paediatric and adult patients to report adverse events.

The overall character, quality, and severity of adverse reactions in paediatric patients is similar to that reported in adult populations from domestic and foreign postmarketing surveillance and other information. Selected commonly reported adverse events in paediatrics include: vomiting, nausea, fever, rash, pruritus and injection associated discomfort and distress. Diarrhea and taste perversion were reported in gastrointestinal studies.

DOSAGE AND ADMINISTRATION

Diagnostic procedures that involve the use of radiopaque imaging 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.

Preparation of the patient will vary with the particular agent used, preference of the radiologist and the type of radiologic procedure performed. Specific radiographic procedures used will depend on the state of the patient and the diagnostic indications.

The combination of volume and concentration of VISIPAQUE to be used should be carefully individualised, accounting for factors such as age, body weight, size of the vessel, rate of blood flow within the vessel, cardiac output, indication for examination, and timing of the X-ray or CT scan. Other factors to be considered are anticipated pathology, degree and extent of opacification required, structure or area to be examined, disease processes affecting the patient, and equipment and technique used.

Usually approximately the same iodine concentration and volume is used as with other iodinated X-ray contrast media in current use, but adequate diagnostic information has also been obtained in some studies with iodixanol injection with somewhat lower iodine concentration.

Generally recommended doses are contained in the following tables. The doses given for intra-arterial use are for single injections that may be repeated:

ADULT DOSAGES

Indication/Investigation	Concentration	Volume
Intra-arterial use		
Arteriographies -		
Selective cerebral	270/320[1] mg I/ml*	5-10 ml per inj.[2]
Aortography	270/320 mg I/ml	40-60 ml per inj.[3]
Peripheral	270/320 mg I/ml	30-60 ml per inj.[3]
Selective visceral i.a.DSA	270 mg I/ml	10-40 ml per inj.[3]
Cardioangiography		
Left ventricle and aortic root inj.	320 mg I/ml	30-60 ml per inj.[4]

Selective coronary arteriography	320 mg I/ml	4-8 ml per inj. [4]
Intravenous use		
Urography	270/320 mg I/ml	40-80 ml[5]
Venography	270 mg I/ml	50-150 ml/leg
CT-enhancement CT of the head - CT of the body –	 270/320 mg I/ml 270/320 mg I/ml	 50-150 ml 75-150 ml

1: Both strengths are documented, but 270 mg I/ml is recommended in most cases.
2: Total dose for combined procedures should not exceed 0.8 g I/kg body weight.
3: Total dose for combined procedures should not exceed 1.2 g I/kg body weight.
4: Total dose for combined procedures should not exceed 0.9 g I/kg body weight.
5: 80 ml may be exceeded in selected cases. Total dose for combined procedures should not exceed 0.46 g I/kg body weight.
* mg I/mL means millligrams of Iodine per millilitre

PAEDIATRIC DOSAGES

Indication/Investigation	Concentration	Volume
Intra-arterial use		
Cardioangiography	* 320 mg I/mL	1-2 ml /kg with max recommended dose of 10 ml/kg. All doses Depending on age, weight and pathology
Intravenous use		
Urography** **Children <7 kg** **Children >7 kg**	 270/320 mg I/ml 270/320 mg I/ml	 2-4 ml/kg 2-3 ml/kg All doses depending on age,weight and pathology (max. 50ml)
CT-enhancement CT of the head and body	 270/320 mg I/ml	 2-3 ml/kg up to 50 ml (in a few cases up to 150 ml must may be given)

Upper Gastointestinal Studies		
Children	270/320 mg I/ml	The dosage must be adjusted individually to allow optimal visualisation 5 ml/kg b.w***. 10-240 ml has been studied

* mg I/mL means millligrams of Iodine per millilitre
** Infants less than 2500 gm were excluded from urography studies.
*** b.w. means body weight

Elderly: As for other adults.

VISIPAQUE may be warmed to body temperature (37°C) before administration.

OVERDOSAGE

Overdosage is unlikely in patients with a normal renal function. The duration of the procedure is important for the renal tolerability of high doses of contrast media (t½~2 hours). In the event of accidental overdosing, the water and electrolyte losses must be compensated by infusion. Renal function should be monitored for at least the next three days. If needed, haemodialysis may be used to remove iodixanol from the patient's system. There is no specific antidote.

Contact poison information center on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

List of excipients

Trometamol,
sodium chloride,
calcium chloride,
sodium calciumedetate,
hydrochloric acid (pH adjustment),
water for injections.

The pH of the product is 6.8 - 7.6.

Incompatibilities

No incompatibility has been found. However, VISIPAQUE should not be directly mixed with other drugs. A separate syringe should be used.

Shelf life

The shelf-lives are:
Glass vials: 3 years in all climatic zones.
Polypropylene bottles: 3 years in climatic zone I and II.

In climatic zone III and IV the shelf-life is shorter, depending on volume and storage conditions.

Special precautions for storage

Protect VISIPAQUE from light. Store below 30°C. Do not freeze.

The product in glass containers and in polypropylene bottles may be stored at 37°C for up to one month prior to use, in a contrast agent warmer utilising circulating warm air. 10 and 20 ml polypropylene ampoules may be stored at 37°C for up to one week prior to use.

Nature and content of container

Glass vials and bottles:
The product is filled in injection vials (20 ml) and infusion bottles (50, 75, 100, 200 and 500 ml). Both containers are made of colourless highly resistant borosilicate glass (Ph.Eur. Type I), closed with chlorobutyl rubber stoppers (Ph.Eur. Type I), and sealed with complete tear off caps with coloured plastic "flip-off" tops.

Polypropylene bottles:
The product is filled in polypropylene bottles. The bottles of 10, 20, 40 and 50 ml are rigid stand-up bottles with a twist-off top.

The bottles of 50, 75, 100, 150, 175, 200 and 500 ml are closed with chlorobutyl rubber stoppers (Ph.Eur. Type I), and supplied with a plastic screw cap which is provided with a tamper proof ring.

Presentations:*

VISIPAQUE (iodixanol) injection 270 mg I/ml

20 ml glass vials, boxes of 10
50 ml glass and PPE bottles, boxes of 10
100 ml glass and PPE bottles, boxes of 10
150 ml glass and PPE bottles, boxes of 10
200 ml glass bottles, boxes of 6
200 ml PPE bottles, boxes of 10
10 ml PPE ampoules, boxes of 10
20 ml PPE ampoules, boxes of 10
40 ml PPE ampoules, boxes of 10
50 ml PPE ampoules, boxes of 10
100 ml bag, 150 ml bag and 200 ml bag

VISIPAQUE (iodixanol) injection 320 mg I/ml

20 ml glass vials, boxes of 10
50 ml glass and PPE bottles, boxes of 10
100 ml glass and PPE bottles, boxes of 10
150 ml glass and PPE bottles, boxes of 10
200 ml glass bottles, boxes of 6
200 ml PPE bottles, boxes of 10
10 ml PPE ampoules, boxes of 10
20 ml PPE ampoules, boxes of 10
40 ml PPE ampoules, boxes of 10
50 ml PPE ampoules, boxes of 10
100 ml bag, 150 ml bag and 200 ml bag

* Some presentations may not be marketed in Australia

Special precautions for disposal and other handling

Like all parenteral products, VISIPAQUE should be inspected visually for particulate matter, discolouration 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.

NAME AND ADDRESS OF SPONSOR

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Australia

DATE OF TGA APPROVAL

May 14, 2010

Therapeutic Goods Administration

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