SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Unilux 370 mg iodine/mL, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 mL contains:
Iopamidol 755 mg
Iodine concentration 370 mg/mL
Excipient with known effect: sodium, contained in 0.48 mg/mL sodium calcium edetate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection
Clear, colourless to pale yellow solution, virtually free from visible particles.

Physical properties:

Viscosity at 37°C	8.0 – 10.0 mPas
pH	6.5 – 7.5
Osmolality	820 – 920 mosmol/kg

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
This medicinal product is for diagnostic use only.
An X-ray contrast medium for:
- angiography (venography, arteriography, phlebography of the extremities)
- digital subtraction angiography (DSA)
- contrast enhancement in computed tomography (CT)
- urography
- retrograde contrast media investigations
- imaging of all body cavities (e.g. arthrography, hysterosalpingography, fistulography)
- intraoperative cholangiography

Unilux 370 is used in adults, adolescents and children from childbirth onwards.

4.2 Posology and method of administration
General information:

The volume and concentration of the administered contrast medium largely depend on the patient's age and weight, cardiac output, renal function, the patient's general condition, the organ/vascular region under investigation, the examination technique selected and technical equipment.
As a rule, the same iodine concentration and the same volume are used as with other conventional iodinated X-ray contrast media.
As with all contrast media, the lowest dose needed to achieve adequate imaging should be used.
In case of doubt, preference should be given to a higher concentration rather than a larger volume.
If diagnostic clarification requires several high individual doses, there should be an interval of 10-15 minutes prior to re-administering the contrast medium, even in patients who are adequately hydrated.

The following dosage recommendations apply as general guidelines.

Angiography:
- *Angiography of the major vessels:* (aortography and selective visceral arteriography:) For this indication, the lower concentrated Unilux 300 is also suitable. Recommended dose:

0.8 -- 1.2 mL/kg/BW Unilux 370. The required single dose depends on the diagnostic scenario, the vascular region being visualised and the radiologist's individual experience.

- *Coronary angiography and laevocardiography:* single dose of 8 – 15mL Unilux 370 as bolus injection. For left ventriculography 50 – 70mL (flow rate 15mL/s)
- *Peripheral arteriography:* For peripheral arteriography of the extremities and imaging of the spinal arteries, 30 - 50 mL Unilux 300 is recommended. As a result of the low osmolality, it has been possible to significantly reduce pain sensitivity (also applies to Unilux 370).
- Children: Depending on height and age, in proportion to the adult dosage.

Digital subtraction angiography (DSA):
For high-contrast imaging of major arteries, pulmonary arteries and arteries of the neck, head, kidney and extremities, intravenous bolus injection of 40 mL Unilux 300 or 370 is recommended (flow rate 17 mL/s into the cubital vein; 17 mL/s into the vena cava). Contact time between the contrast medium and venous wall can be reduced with immediate subsequent administration of 20 - 40 mL isotonic sodium chloride solution as a bolus injection. Unlike intravenous digital subtraction angiography, smaller volumes and lower iodine concentrations are sufficient for intra-arterial DSA. Consequently, this method is recommended even for patients with impaired renal function.
Children: Depending on height and age, in proportion to the adult dosage.

Computed tomography (CT):
For contrast enhancement of tumours and other lesions in cranial CT, 1 – 1.5 mL/kg BW Unilux 370 is administered intravenously. Initiation of the scan primarily depends on the diagnostic scenario. In whole-body CT, the required amounts of contrast medium and rate of administration depend on the organs under investigation, the diagnostic scenario and, in particular, the equipment available.
With devices that work more slowly, infusions should be given preference, while injections should be preferred for rapid scanners.
Children: Depending on height and age, in proportion to the adult dosage.

Intravenous urography (IVU):

- *Adults:* In adult patients with normal body weight, a dose of around 0.3 g iodine/kg BW should not be exceeded; this is equivalent to approximately 0.8 mL/kg BW of Unilux 370, if the diagnostic scenario also requires adequate filling of the ureters. Dose escalation is possible if deemed necessary in special cases, e.g. in cases of obesity or impaired renal function. In patients who are overweight or with impaired renal function, the dose should be increased to 0.45 - 0.6 g iodine/kg BW. For Unilux 370, this is equivalent to a dose of 1.2 – 1.6 mL/kg BW.
- *Children:* The physiologically poor concentrating ability of the still immature nephron of juvenile kidneys demands relatively high doses of contrast medium, e.g. with the use of Unilux 370:
  Newborns: 1.5 g I/kg BW is equivalent to 4.0 mL/kg BW
  Babies: 1.0 g I/kg BW is equivalent to ~ 2.7 mL/kg BW
  Infants: 0.5 g I/kg BW is equivalent to ~1.4 mL/kg BW
- *Rate of administration:* The excellent tolerability of Unilux 370 allows rapid bolus injection within a few seconds, resulting in good parenchymal opacification.
- *Recording times:* Imaging of the renal parenchyma is optimal when recorded immediately after administration has ended. For imaging of the renal pelvis and lower urinary tract, the first image is taken 3 – 5 minutes and the second 10 – 12 minutes p.i. The earlier time should be chosen for younger patients and the later time for older patients. For infants and babies, it is recommended that the first image be taken as early as approximately 2 minutes p.i. Later recordings may be required in patients with impaired renal function.

Retrograde urography:
Unilux 370 can be used undiluted for retrograde urography and does not lead to any signs of irritation. Particularly in this investigation, the contrast medium should be well warmed in advance, as the cold stimulus is perceived as painful.

Method of administration:

- For intravenous, intra-arterial or direct administration
- Instillation into all body cavities

Notes on use:

- The contrast medium should be warmed to body temperature.
- Unilux must not be drawn up until immediately prior to use.
- Caution is indicated when injecting contrast media, in order to avoid extravasation.

4.3 Contraindications

- hypersensitivity to the active substance and/or iodine or to any of the excipients of the product listed in section 6.1.
- manifest hyperthyroidism.
- Hysterosalpingography must not be performed in the presence of acute inflammatory processes in the pelvic cavity.
- manifest tetany.

4.4 Special warnings and precautions for use

Diagnostic procedures requiring the use of contrast media should be performed only under the supervision of trained personnel with detailed knowledge of the respective procedure. In order to be able to react immediately in an **emergency**, a secure vascular access should be ensured (e.g. indwelling cannula). For the treatment of possible complications during use, as well as for emergency treatment in the event of a serious reaction to the contrast medium itself, the requisite resources should be available. For emergency resuscitation, appropriately trained personnel - as well as the requisite mechanical and pharmacological resources - must be available.

Particular caution is advised in the following cases:

- hypersensitivity to iodinated contrast media
- severe renal impairment, particularly if accompanied by severe liver damage. The risks of contrast medium administration are increased considerably when creatinine levels exceed 2-3 mg/dL.
- chronic diabetes, particularly in the presence of azotaemia
- patients with cardiovascular impairment
- multiple myeloma (Kahler's disease, plasmacytoma, Waldenstrom's macroglobulinaemia)
- suspected phaeochromocytoma
- advanced cerebral arteriosclerosis and hypertension
- pulmonary emphysema
- cerebral seizure
- thyrotoxicosis
- very poor general state of health

In all of these conditions, there must be a compelling indication for use and the investigation should only be carried out when the anticipated success outweighs the risk.

Information on sodium content:
This medicinal product contains less than 1 mmol sodium (23 mg) per maximum recommended dose (regardless of the respective therapeutic indication), i.e. essentially sodium-free.

Precautions and instructions for the safe use of iodinated contrast media.

- **Hypersensitivity to iodinated contrast media:**
  As with all other contrast media, this product may cause pseudoallergic (allergoid), anaphylactic reactions or other manifestations of allergic reactions, with nausea, vomiting, dyspnoea, erythema, urticaria and hypotension. There have been occasional reports of serious reactions with fatal outcome.

Such events are not predictable in individual cases. The patient should be informed that allergic reactions may even occur several days after use. In this case, a physician should be consulted.

A prior history of allergy, asthma or adverse reactions during previous similar examinations indicates that particular caution is required. In these patients, the benefit must clearly outweigh the risks and pre-treatment with antihistamines (H_1-receptor blockers) or corticosteroids should be considered to prevent or minimise possible allergic reactions.

In patients with asthma, there is a greater risk of bronchospasm-induced reactions following use of contrast media, this applies in particular to patients taking beta-blockers.

It is not recommended that sensitivity tests be performed in patients with suspected or known contrast medium hypersensitivity, as severe or fatal reactions to contrast media cannot be predicted with sensitivity tests.

- Prior to administration of any contrast medium, a precise **history** should be obtained, including important laboratory parameters (e.g. allergic history, possible pregnancy, ECG, renal and hepatic function parameters).
- Patients with **congestive heart failure** should be monitored for several hours following the examination for delayed haemodynamic disturbances, which may be associated with a transient increase in the circulating osmotic load. All other patients should be observed for 20-30 minutes following the examination, as most adverse events occur within this period.
- In patients undergoing **angiocardiography**, special attention should be paid to the right heart status and pulmonary circulation. Existing right heart failure and pulmonary hypertension may precipitate bradycardia and systemic hypotension when the organic iodine solution is injected. Right heart angiography should be performed only when absolutely necessary. Particular caution should be exercised when injecting contrast media into the heart chambers, especially in cyanotic newborns with pulmonary hypertension and impaired heart function.
- During **intracardiac and/or coronary arteriography**, ventricular arrhythmias may occur in rare cases.
- **Intra-arterial contrast media injections** may lead to vasospasms with subsequent cerebral ischaemic phenomena.
- Extreme caution should be exercised when **injecting contrast media into the heart chambers**, especially in cyanotic newborns with pulmonary hypertension and impaired heart function.
- In **angiography**, there is a possibility of dislodging plaque or damaging or perforating the vascular wall. These risks should be considered during catheter manipulation and contrast medium injection. Test injections to ensure proper catheter placement are recommended. In examinations of the aortic arch, the catheter tip must be positioned carefully to avoid hypotension, bradycardia and CNS injury due to excess pressure transmitted from the injector pump to the brachiocephalic branches of the aorta.
- In patients with homocystinuria, angiography must be avoided whenever possible due to an increased risk of thrombosis and embolism.
- In patients undergoing **peripheral angiography**, there should be pulsation in the artery to be injected with the X-ray contrast medium. In patients with thromboangiitis obliterans or ascending infections in combination with severe ischaemia, angiography should be performed only with extreme care, if at all. Particular caution is required in patients undergoing venography, if phlebitis, severe ischaemia, local infections or complete venous occlusion are suspected.
- Heightened responsiveness is likely in **patients in a state of apprehensive expectation**. In such patients, premedication with tranquilisers, e.g. diazepam, can be performed.
- Before and after administration of contrast media, **adequate hydration** should be ensured. Fluid intake must not be restricted and disturbances of the fluid and electrolyte balance must be corrected. This particularly applies to patients with diabetes mellitus, renal dysfunction, severe hepatic or myocardial impairment or multiple myeloma, polyuria, oliguria,

hyperuricaemia and severe systemic disease, as well as in babies, infants, the elderly, as well as patients in a very poor general condition.

- To prevent crises in patients with **sickle cell disease**, adequate hydration must be ensured and only a minimal volume of low concentration should be used.
- **Intravascular administration of contrast media** should, if possible, be performed with the patient in the supine position. Following administration of the contrast medium, the patient should remain under observation for at least another 1 hour, since experience shows that the majority of severe incidents occur within this time. Severe delayed reactions can also occur in isolated cases.
- There is also an increased risk for patients with Waldenstrom's paraproteinaemia, multiple myeloma or severely impaired liver and renal function. In these patients, adequate hydration is recommended after administration of the contrast medium.
- With non-ionic contrast media, **extravasated medium** leads to tissue reactions on rare occasions. Cold compresses and raising the affected extremity are adequate countermeasures.
- It has been established *in vitro* that the inhibitory effect on haemostatic mechanisms is less marked with non-ionic contrast media, when compared with ionic contrast media at a similar concentration. For this reason, prolonged contact between blood and contrast media in syringes and catheters should be avoided in angiographic examinations and catheters should be flushed more frequently. Factors such as the length of examination, catheter and syringe material, underlying disease and co-medications may contribute to the development of thromboembolic events. Extremely careful angiographic techniques are therefore recommended, with close monitoring of guide wire and catheter manipulation, use of manifold systems and/or three-way stopcocks. In addition, the catheter should be frequently flushed with heparinised saline solution and the length of examination restricted as much as possible. Use of plastic syringes seems to reduce the **clotting risk**.
- As all iodinated contrast media react with **copper-containing surfaces** (alloys such as bronze, brass), contact between Unilux and such objects, devices, etc. should be avoided.

Special warnings:

- **Thyroid dysfunction**:
  All iodinated contrast media may precipitate hyperthyroidism in predisposed patients in isolated cases. In patients with suspected hyperthyroidism, thyroid function must be checked prior to administering Unilux. In patients with known hyperthyroidism, thyrostatic prophylaxis must be administered. In patients having received treatment for Basedow's disease, there is a possibility of hyperthyroid recurrence – hence, there should be a strict indication for use in these cases.
- **Renal dysfunction**:
  Particularly after intravascular administration, **contrast medium-induced nephropathy** may occur (transient renal dysfunction and even kidney failure). The risks of contrast media administration increase considerably when creatinine levels are above 2-3 mg/dL.
  Patients with severe hepatic or renal impairment, or concomitant impairment of both organs, should be investigated only when absolutely necessary. In the case of repeat investigation, a period of 5 to 7 days should be respected. In patients with impaired renal function, administration of potential nephrotoxic medicines should be avoided until complete excretion of the contrast medium and renal function parameters should be observed. Subsequent examination with the contrast medium should proceed only when renal function has regained its baseline level. Particularly in patients with diabetes mellitus on metformin therapy, pre-existing renal dysfunction or contrast medium-induced renal dysfunction may precipitate lactic acidosis (see section 4.5).
- **CNS disturbances**:
  In **patients with a confirmed history of cerebral seizures**, careful consideration of the benefits and risks of the examination is necessary. In these patients, prophylaxis with phenobarbital is effective. If epileptic seizures occur, diazepam (5 - 10 mg slow IV) is recommended, followed by phenobarbital (0.2 g IM) 20 - 30 minutes after the seizure has subsided. Discontinuation of on-going anticonvulsant therapy is not required. In some cases, anticonvulsant therapy can be intensified for 48 hours prior to the examination.

- Iopamidol should be used with caution in patients with hypercalcaemia, symptomatic cerebrovascular disease, recent stroke or frequent temporary ischaemia, altered permeability of the blood-brain barrier, increased intracranial pressure, suspected intracranial tumour, abscess or haematoma/bleeding, history of seizures and alcohol abuse.
- **Phaeochromocytoma**
  Due to the risk of hypertensive crisis, premedication with α-receptor blockers is recommended for patients with phaeochromocytoma.
- **Contrast induced encephalopathy**
  Encephalopathy has been reported with the use of iopamidol (see section 4.8). This may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema within minutes to hours after administration and generally resolves within days. Factors which increase blood-brain barrier permeability will ease the transfer of contrast media to brain tissue and may lead to possible CNS reactions, for instance encephalopathy. If contrast encephalopathy is suspected, iopamidol should not be re-administered and appropriate medical management should be initiated.
- **Alcoholism/drug addiction**
  In this patient group, there is a greater risk of neurological reactions due to increased permeability of the blood-brain barrier and/or a possibly low stimulus threshold.
- **Myasthenia gravis**
  The symptoms of myasthenia gravis can be enhanced by iodinated contrast media.
- **Severe cutaneous adverse reactions**
  Severe cutaneous adverse reactions (SCARs), such Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (Lyell's syndrome or TEN) and acute generalised exanthematous pustulosis (AGEP), which can be life threatening, have been reported in patients administered Scanlux (see section 4.8, undesirable effects). At the time of initiation, patients should be advised of the signs and symptoms and monitored closely for severe skin reactions. If signs and symptoms suggestive of these reactions appear, further use of Scanlux should be withheld. If the patient has developed a severe cutaneous adverse reaction with the use of Unilux, Unilux must not be re-administered in this patient at any time.

Use in specific patient groups
Newborns, children
Babies (< 1 year) and, in particular, newborns are particularly susceptible for disturbances of the electrolyte balance and haemodynamic changes. Careful attention should therefore be paid to the dose to be used, the specificities of the examination and the patient's status.
Transient thyroid suppression or hypothyroidism has been observed in children after exposure to iodinated contrast media. Following a diagnostic procedure, this has been more frequently observed in neonates and premature infants and also following procedures associated with higher doses. Neonates may also be exposed via maternal exposure. In neonates, especially preterm infants, who have been exposed to iopamidol, either through the mother during pregnancy or in the neonatal period, it is recommended to monitor thyroid function. If hypothyroidism is detected, the need for treatment should be considered and thyroid function should be monitored until normalised.

Elderly ≥ 65 years
The elderly are at particular risk of adverse reactions due to reduced physiological functions, especially at high contrast medium doses. Myocardial ischaemia, severe arrhythmias and premature ventricular complexes are more likely to occur in these patients, as is the probability of acute renal failure.

Women of child-bearing potential
For radiological investigations in women of child-bearing potential, appropriate investigational methods and measures must be used, regardless of whether or not a contrast medium is used.

Procedures in the event of a contrast medium-related incident

Monitoring
Heart rate and cardiac rhythm, pulsoximetry, blood pressure (continuous intra-arterial measurement in case of shock)

Treatment (in accordance with ESUR guidelines, version 7.0; ESUR= European Society of Urogenital Radiology)

Symptoms	**Treatment**
Nausea/vomiting	Transient: supportive measures Severe, persistent: consider suitable antiemetics
Laryngeal oedema, urticaria	Laryngeal oedema 1. Oxygen via a breathing mask (6 - 10 L/min) 2. Adrenaline IM (1:1,000), 0.5 mL (0.5 mg) for adults, repeat if necessary children aged 6-12 years: 0.3 mL (0.3 mg) IM; children under 6 years: 0.15 mL (0.15 mg) IM Urticaria - isolated, transient: supportive treatment and observation - isolated, persistent: consider treatment with appropriate H_1 antihistamines (IM or IV). Light-headedness and/or hypotension can occur. - severe intensity: consider treatment with adrenaline 1:1,000, 0.1-0.3 mL (0.1-0.3 mg) IM for adults; for children aged 6-12 years: half the adult dose; for children under 6 years, 25% the adult dose. Repeat if necessary.
Bronchospasm	1. Oxygen via a breathing mask (6-10 L/min) 2. Beta-2 agonist via metered-dose inhaler (2-3 deep inhalations) 3. Adrenaline: dosage according to age and blood pressure. If blood pressure is normal: 0.1 – 0.3 mL (0.1 -0.3 mg) IM (in CHD and elderly patients, select a lower dose). For children: 0.01 mg/kg up to a maximum of 0.3 mg. If blood pressure is low: 0.5 mL (0.5 mg) IM; for children aged 6-12 years: 0.3 mL (0.3 mg) IM; for children under 6 years: 0.15 mL (0.15 mg) IM
Hypotension	Isolated hypotension 1. Raise the patient's legs 2. Oxygen via a breathing mask (6-10 L/min) 3. Fluid administration IV (physiological saline solution, Ringer's lactate solution) 4. If no response: adrenaline 1:1,000, 0.5 mL (0.5 mg) IM, repeat if necessary. For children aged 6-12 years: 0.3 mL (0.3 mg) IM; for children under 6 years: 0.15 mL (0.15 mg) IM Vagal reaction (hypotension and bradycardia) 1. Raise the patient's legs 2. Oxygen via a breathing mask (6-10 L/min) 3. Atropine 0.6-1.0 mg IV, repeat if necessary after 3-5 minutes, maximum total dose 3 mg (0.04 mg/kg) for adults. For children: 0.02 mg/kg IV (0.6 mg max. per injection); repeat if necessary up to a maximum total dose of 2 mg. 4. Fluid administration IV (promptly give physiological saline solution or Ringer's lactate solution)
Pulmonary oedema	Intubation, continuous positive airway pressure with oxygen, furosemide 40 mg IV

Cardiovascular and respiratory arrest	Generalised anaphylactoid reaction 1. Alert the resuscitation team 2. Clear the airways via aspiration, if required 3. In case of hypotension, raise the patient's legs 4. Oxygen via a breathing mask (6-10 L/min) 5. Adrenaline IM (1:1,000), 0.5 mL (0.5 mg) for adults, repeat if necessary; for children aged 6-12 years: 0.3 mL (0.3 mg) IM; for children under 6 years: 0.15 mL (0.15 mg) IM 6. Fluid administration IV (e.g. physiological saline solution, Ringer's lactate solution) 7. H_1 blockers (e.g. diphenhydramine 25-50 mg IV)

In the event of shock, cardiac arrhythmias and adrenaline use, a **defibrillator must be readily available.**
Following serious incidents, 24-hour monitoring and/or ICU treatment of the patient is generally required.

4.5 Interaction with other medicinal products and other forms of interaction

- **Biguanides (metformin)**

In diabetic patients with moderately impaired renal function receiving treatment with oral antidiabetics of the biguanide class (e.g. metformin) and electively scheduled to undergo an examination using contrast media, biguanide should, in order to avoid lactate acidosis, be discontinued 48 hours prior to administration of the contrast medium and should only be resumed 48 hours thereafter if the serum creatinine level/eGFR has returned to its pre-examination value (see section 4.4).
In emergency patients with impaired or unknown renal function, the physician should weigh up the risks and benefits of a contrast medium examination. Treatment with metformin should be discontinued at the time of the contrast medium administration. Following the examination, the patient should be monitored for signs of lactate acidosis. Therapy with metformin can be resumed 48 hours after administration of the contrast medium if the serum creatinine level/eGFR has returned to its pre-examination value.
Patients with normal renal function can keep taking metformin without any modifications.

- **Neuroleptics, analgesics, antihistamines, antiemetics and phenothiazine-type sedatives**

As these medicinal products may promote the precipitation of seizures, they should be discontinued 48 hours prior to using iodinated contrast media. Treatment can be resumed 24 hours after the examination.

- **Beta-blockers/antihypertensives**

Hypersensitivity reactions may occur in a more exaggerated form in patients taking beta-blockers, particularly in the presence of bronchial asthma. Heart patients and/or hypertensive patients treated with diuretics or ACE inhibitors are at greater risk of adverse reactions when administered an iodinated contrast medium.
Beta-blockers can interfere with the effect of treatment of contrast medium-induced bronchospasms.

- **Interferon/interleukin**

Previous or concomitant treatment with interferons or interleukins is associated with an increased risk of delayed reactions. Following administration of iopamidol, atypical adverse reactions such as erythema, fever and influenza symptoms have been reported in patients treated with interleukin-2.
Following administration of iopamidol following papaverine, arterial thrombosis has been reported.
Administration of vasopressors significantly enhances the neurological effects of intra-arterial contrast media.
Contrast media may affect the results of laboratory tests on bilirubin, proteins or inorganic compounds (e.g. iron, copper, calcium and phosphate). These substances should not be tested on the same day after administration of the contrast medium.

- **Effect on diagnostic tests:**

Examinations with iodinated contrast media may reduce the capacity of thyroid tissue to take up radioisotopes for up to 2-6 weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy

Only in cases where the indication for use is critical, after exhaustion of all other diagnostic options. The safety of iopamidol injections during pregnancy has not yet been established. As radiation exposure during pregnancy should be avoided in any case, regardless of whether or not a contrast medium is used, the benefit of X-ray examination must be carefully considered. Apart from radiation exposure in the foetus, sensitivity of the foetal thyroid to iodine must also be taken into account in the benefit-risk assessment for use of iodinated contrast media. If pregnant women are given iodinated contrast media, neonatal thyroid function must be checked within the first week after delivery (see section 4.4).

Breastfeeding

Small amounts of iodinated X-ray contrast media are excreted in breast milk. However, discontinuation of breastfeeding is not necessary.

Fertility

For radiological investigations in women of child-bearing potential, appropriate investigational methods and measures must be used regardless of whether or not a contrast medium is used.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions are generally mild to moderate and transient. However, rare, severe and life-threatening reactions, in some cases leading to death, have been reported.

After intravascular use, reactions occur in most cases within a few minutes following administration. However, delayed reactions, usually affecting the skin, can also occur, which set in within 2-3 days and more rarely within 7 days after administration of the contrast medium.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with Unilux administration (see section 4.4).

In clinical studies, the most commonly reported adverse reactions after intravascular use were headache (1.5%), nausea (1.2%) and hot flushes (3.5%).

Adverse reactions reported from clinical studies on 2,680 adult participants and 35 children, as well as adverse reactions known from observational studies, are listed in the following tables according to frequency and classified by MedDRA system organ class.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

4.8.1 Intravascular use

System organ classes	**Adverse reactions**			
	Clinical studies			**Post-marketing observations**
	Common (≥1/100 to <1/10)	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known***

Blood and lymphatic system disorders				Thrombocytopenia
Immune system disorders				Anaphylaxis, anaphylactoid reaction
Psychiatric disorders			Confusion	
Nervous system disorders	Headache	Dizziness, Abnormal sense of taste	Paraesthesia	Coma, transient ischaemic attack, syncope, impaired consciousness or loss of consciousness, convulsion, hemiplegia, contrast induced encephalopathy **
Eye disorders				Temporary blindness, visual disturbances, conjunctivitis, photophobia
Cardiac disorders		Cardiac arrhythmias, such as extrasystoles, ventricular tachycardia, ventricular or atrial fibrillation ***	Bradycardia	Myocardial ischaemia or infarction, heart failure, cardiorespiratory arrest, tachycardia, Kounis syndrome
Vascular disorders		Hypotension, hypertension, flush		Circulatory collapse or shock
Respiratory, thoracic and mediastinal disorders			Pulmonary oedema, asthma, bronchospasm	Respiratory arrest, respiratory insufficiency, acute shock lung (ARDS), respiratory distress, apnoea, laryngeal oedema, dyspnoea

Gastrointestinal disorders	Nausea	Vomiting, diarrhoea, abdominal pain, dry mouth		Increased salivation, salivary gland enlargement
Skin and subcutaneous tissue disorders		Rash, urticaria, pruritus, erythema, increased sweating		Facial oedema, Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		Back pain	Muscle cramps	Musculoskeletal pain, muscle weakness
Renal and urinary disorders		Acute kidney failure		
General disorders and administration site conditions	Sensation of heat	Chest pain, injection-site pain, fever, sensation of cold		Rigor, pain, malaise
Investigations		Elevated blood creatinine level		ST-segment depression in the electrocardiogram

* As the reactions were not observed in clinical trials with 2,548 patients, the best estimate of their relative frequency is 'rare' (> 1/10,000 to < 1/1,000).
The most appropriate MedDRA term is used to describe a certain reaction and its symptoms and associated manifestations.
** Contrast induced encephalopathy may manifest with symptoms and signs described in section 4.4.
*** Cardiac arrhythmias mostly occur after cardiac angiography and after catheter examination of the coronary arteries.

As a complication of catheter examination of the coronary vessels, cases of coronary artery thrombosis have been observed.

Other cardiac reactions, for which there is a risk associated with heart examinations, include dissection of the coronary artery.

Anaphylactic shock (anaphylactoid reactions/hypersensitivity) may occur, manifesting as mild localised or more diffuse angioedema, tongue oedema, laryngospasm or laryngeal oedema, dysphagia, pharyngitis and throat tightness, pain in the throat and larynx, cough, conjunctivitis, rhinitis, sneezing, sensation of heat, increased sweating, asthenia, dizziness, pallor, dyspnoea, wheezing, bronchospasm and moderate hypotension. Skin reactions in the form of various types of skin rash, diffuse erythema, diffuse blisters, urticaria and pruritus may occur. These reactions occur regardless of the dose administered and method of administration and may be the first signs of an imminent state of shock. Administration of the contrast medium must be terminated immediately and, if necessary, specific treatment initiated via a venous access.

More serious reactions of the cardiovascular system may be: vasodilation with marked hypotension, tachycardia, dyspnoea, agitation, cyanosis and loss of consciousness, which may progress to cardiorespiratory arrest with fatal outcome. Onset of these events may be rapid and they require aggressive cardiopulmonary resuscitation.
Circulatory collapse may occur as the only and/or initial sign without respiratory symptoms or any other of the signs and symptoms listed above.

At the injection site, pain and swelling may occur. In very rare cases, extravasation of contrast media has led to inflammation (manifested by local erythema, oedema and blisters), skin necrosis and compartment syndrome.

As with other iodinated contrast media, mucocutaneous syndromes such as Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema multiforme have been identified in very rare cases after administration of iopamidol.

Children
Iopamidol has a similar safety profile in children and adults.
Cases of transient neonatal hypothyroidism have been reported with Iopamidol in very low birth weight infants.

4.8.2 Use in body cavities
The majority of reactions do not occur until a few hours after administration of the contrast medium, as the latter is only slowly absorbed from the site of administration and distributed in the body.
Blood amylase elevations after ERCP are common. In very rare cases, pancreatitis has also been observed.
The reactions reported during arthrography and fistulography mostly manifest as signs of irritation overlapping with existing tissue inflammation.
Systemic hypersensitivity is rare. It is usually mild and manifests in the form of skin reactions. However, the possibility of severe anaphylaxis-like reactions cannot be excluded.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via *Bundesamt für Sicherheit im Gesundheitswesen* (Federal Office for Safety in Health Care), Traisengasse 5, 1200 VIENNA, Austria, fax: + 43 (0) 50 555 36207, website: http://www.basg.gv.at/.

4.9 Overdose
Doses in excess of the specific dose recommendations in section 4.2 are not recommended, as they can lead to life-threatening undesirable effects.

In the event of an overdose, the patient must be observed and treated symptomatically. Iopamidol can be dialysed.

If an inadvertent intravascular overdose occurs in humans, fluid and electrolyte loss must be corrected by an infusion. Renal function should be monitored for at least three days.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: water-soluble, nephrotropic, low osmolar X-ray contrast media.
ATC code: V08AB04
Unilux (Iopamidol) is a non-ionic, low-osmolar X-ray contrast medium, capable of passing through the kidneys. It is available as a stable, ready-to-use solution at concentrations of 300 and 370 mg I/mL.
Iopamidol, a contrast-producing agent, is characterised by the following:
- good general tolerability
- low general toxicity
- good neural tolerability

- little effect on cardiovascular functions
- good local and endothelial/intimal tolerability
- pain-free administration
- little influence on clotting, fibrinolysis or complement activation
- high contrast density in the lower urinary tract.

5.2 Pharmacokinetic properties

Absorption

Iopamidol does not undergo metabolism, is not stored in the liver and has extremely low plasma protein binding.

Elimination

Iopamidol is eliminated via glomerular filtration in chemically unchanged form. Its elimination half-life is around 2 hours in patients with healthy kidneys. After 24 hours, iopamidol is almost completely excreted with the urine. In patients with severely impaired renal function, the elimination half-life can be as much as 70 hours approx.; it can be reduced to about 3.5 hours with a 4-hour haemodialysis session. Excretion of the contrast medium may also be delayed in patients with severe renal impairment and concomitant hepatic dysfunction.

Distribution

Iopamidol is unable to penetrate the blood-brain barrier and crosses the placental barrier to a very limited extent.

5.3 Preclinical safety data

Acute toxicity with intravenous administration was tested on mice, rats, rabbits and dogs; it ranged between 19.6 (rabbit) and 44.5 (mouse) g/kg iopamidol or 9.6 and 21.8 g I/kg body weight. With daily administration over 4 weeks, no toxic symptoms were revealed in rats at dosages up to 6.0 g/kg or in dogs at dosages up to 8.2 g/kg.

In teratogenicity and fertility studies, no visible effects of treatment were found at daily doses of 8.2 g/kg in rats or 4.1 g/kg in rabbits. Reproductive function was not affected in either animal species, either in female or male animals. No mutagenic properties of iopamidol were demonstrated during *in vitro* tests.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol, hydrochloric acid for pH adjustment, sodium calcium edetate, water for injections.

6.2 Incompatibilities

Unilux must not be mixed with other medicinal products.

6.3 Shelf life

3 years

Stability after opening:

For single use only.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light. Protect from X-rays.

6.5 Nature and contents of container

Unilux 370 mg I/mL is available in 50 mL, 75 mL, 100 mL, 200 mL and 500 mL clear glass vials (glass type II) with a bromobutyl rubber stopper and aluminium cap (“flip off” cap), either individually or in the following pack sizes:

10 x 50 mL, 10 x 75 mL, 10 x 100 mL, 10 x 200 mL, 5 x 500 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

In rare cases, the contrast medium may crystallise in the original container. The contrast medium must be discarded in such cases.

Use only clear and colourless to almost colourless solutions.
Intended for single use only. After opening, use immediately.
Any contrast medium solution not used in one examination session must be discarded, as low-osmolar contrast media represent a good breeding ground for pathogenic germs.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
In addition, the following instructions apply to use of the 500 mL infusion vial:
Unilux 500 mL may only be used in conjunction with an injector. The tube section connecting the injector to the patient (patient tube) must be exchanged after each examination, as contamination with blood cannot be excluded.
Instructions for use by the respective equipment manufacturer must be observed.
At the end of the examination, any contrast medium remaining in the vial, plus the withdrawal cannula, must be discarded.

7. MARKETING AUTHORISATION HOLDER

Sanochemia Pharmazeutika GmbH
Landegger Straße 7
2491 Neufeld an der Leitha
Austria

8. MARKETING AUTHORISATION NUMBER(S)

1-30683

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/10/2011

10. DATE OF REVISION OF THE TEXT

February 2022

GENERAL CLASSIFICATION FOR SUPPLY
medicinal product subject to non-renewable medical prescription, available from pharmacies only