Bundesamt für Sicherheit
im Gesundheitswesen

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Betreff: Iodixanol – hältige Arzneispezialitäten – Änderungen der Fach- und Gebrauchsinformationen aufgrund des HBD – PSUR Worksharing Projektes

Sehr geehrte Damen und Herren,

basierend auf der Evaluierung des PSURs im EU-HBD-worksharing Projekt (Verfahrensnummer: NO/H/PSUR/0016/001) kommt es zu der Empfehlung, folgende Ergänzungen in die **Fach- und Gebrauchsinformation** aller Iodixanol– hältigen Arzneispezialitäten aufzunehmen.

Sollten diese bereits aufgenommen worden sein, betrachten Sie dieses Schreiben als gegenstandslos.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Special precautions for use of non-ionic contrast media in general

Hypersensitivity

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

The 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.

The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/ anaphylactoid reactions should always be considered. The majority of serious undesirable occur within the first 30 minutes. Late onset (that is 1 hour or more after application) hypersensitivity reactions can occur.

Patients should be observed for at least 30 minutes after administration of VISIPAQUE.

Patients using beta blockers may present with atypical symptoms of hypersensitivity which may be misinterpreted as a vagal reaction.

Coagulopathy

Nonionic, iodinated contrast media inhibit blood coagulation in vitro less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing contrast media including nonionic media. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angio-cardiographic procedures with both ionic and nonionic contrast media. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended, including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions, and minimizing the length of the procedure.

Advanced life support facilities should be readily available.

Care should be taken in patients with homocystinuria. (Risk for thromboembolism)**.**

Hydration

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

Cardio-circulatory reactions

Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias. Rarely severe life-threatening reactions and fatalities of cardiovascular origin such as cardiac-, cardio-respiratory arrest and myocardial infarction have occurred.

CNS disturbances

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 lowered threshold for seizures and neurological reactions. In regard to intravascular application care should be taken in patients with acute stroke or acute intracranial bleeding, in patients with altered blood brain barrier, cerebral edema or acute demyelinisation.

Renal reactions

Major risk factor for contrast medium-induced nephropathy is underlying renal dysfunction.
Diabetes mellitus and the volume of iodinated contrast medium administered are contributing factors in the presence of renal dysfunction. Additional concerns are dehydration, advanced arteriosclerosis, poor renal perfusion and the presence of other factors that may be nephrotoxic, such as certain medications or major surgery.

To prevent acute renal failure following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk.

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

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

Iodinated contrast agents can be used by patients on haemodialysis as the agents are removed by the dialysis process.

Diabetic patients receiving 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 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 medium 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.

Impaired renal and hepatic function
Particular care is required in patients with severe disturbance of both renal and hepatic function as they may have significantly delayed contrast medium clearance.

Myasthenia gravis
The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis.

Phaeochromocytoma

In patients with phaeochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis.

Disturbances in thyroid function

Patients at risk of thyrotoxicosis should be carefully evaluated before any use of iodinated contrast medium. Special care should be exercised in patients with hyperthyroidism. Patients with multinodular ~~goiter~~ goitre may be at risk of developing hyperthyroidism following injection of iodinated contrast media.

Paediatric population

One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media.

Thyroid function should be checked in neonates during the first week of life, following administration of iodinated contrast agents to the mother during pregnancy. Repeat testing of thyroid function is recommended at 2 to 6 weeks of age, particularly in low birth weight newborn or premature newborn. See also section 4.6.

Extravasation

In case of extravasation it is likely that VISIPAQUE, due to its isotonicity, gives rise to less local pain and extravascular oedema than hyperosmolar contrast media. Elevating and cooling the affected site is recommended as a routine measure; 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 occur within this time. However, experience shows that hypersensitivity reactions may appear up to several hours or days post injection. ~~Routine care after myelography should include supine position with head up for a while. Afterwards the patient should not be left alone for 12 to 24 hours.~~

Intrathecal use

Following myelography the patient should rest with the head and thorax elevated by 20° for one hour. Thereafter he/she may ambulate carefully but bending down must be avoided. The head and thorax should be kept elevated for the first 6 hours if remaining in bed. Patients suspected of having a low seizure threshold should be observed during this period. Outpatients should not be completely alone for the first 24 hours.

Hysterosalpingography

Hysterosalpingography should not be performed during pregnancy or in the presence of acute pelvic inflammatory disease (PID).

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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 metformin (see section 4.4).

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

There is some evidence that use of beta blockers is a risk factor for anaphylactoid reactions to X-ray contrast media (severe hypotension has been seen with X-ray contrast media on beta blocker therapy).

4.6 Fertility, pregnancy and lactation

Pregnancy:
The safety of VISIPAQUE for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or fetus, the course of gestation and peri- and postnatal development. 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.
Thyroid function should be checked in neonates during the first week of life, following administration of iodinated contrast agents to the mother during pregnancy. Repeat testing of thyroid function is recommended at 2 to 6 weeks of age, particularly in low birth weight newborn or premature newborn.

Breast-feeding:
Contrast media are poorly excreted in human breast milk and minimal amounts are absorbed by the intestine. Breast feeding may be continued normally when iodinated contrast media are given to the mother.
~~Iodinated contrast agents are only excreted in breast milk in very small amounts. Although isolated administration to the mother involves a minor risk of adverse reaction in the infant, it is advisable to stop breast feeding for 24 hours after administration of an iodinated contrast agent, and to discard the pumped breast milk~~

4.7 Effects on ability to drive and use machines

No studies on the ability to drive or use machines have been performed. However, it is not advisable to drive a car or use machines during the first 24 hours following intrathecal examination.

4.8 Undesirable effects

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

Undesirable effects associated with VISIPAQUE are usually mild to moderate and transient in nature. Serious reactions as well as fatalities are only seen on very rare occasions, these may include acute-on-chronic renal failure, acute renal failure, anaphylactic or anaphylactoid shock, hypersensitivity reaction followed by cardiac reactions (Kounis' syndrome), cardiac or cardio-respiratory arrest and myocardial infarction. Cardiac reaction may be promoted by the underlying disease or the procedure.

Hypersensitivity reactions may present as respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus, severe skin reactions, angioneurotic oedema, hypotension, fever, laryngeal oedema, bronchospasm or pulmonary oedema. In patients with autoimmune diseases cases of vasculitis and SJS-like syndrome were observed.
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.

The frequencies of undesirable effects are defined as follows:
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

The listed frequencies are based on internal clinical documentation and published studies, comprising more than 48,000 patients.

Intravascular administration:
Blood and lymphatic system disorders
Not known: Thrombocytopenia

Immune system disorders:
Uncommon: Hypersensitivity
Not known: Anaphylactoid reaction, anaphylactoid shock; ~~severe pustular or bullous skin reactions~~

Psychiatric disorders:
Very rare: Agitation, anxiety
Not known: Confusional state

Nervous system disorders:
Uncommon: Headache
Rare: Dizziness
Very rare: Cerebrovascular accident, ~~S~~sensory abnormalities including taste disturbance, paraesthesia,syncope
Not known: Coma, ~~M~~motor dysfunction, disturbance in consciousness, convulsion , transient contrast induced encephalopathy (including amnesia, hallucination ~~and other neurological symptoms~~), tremor

Eye disorders:
Very rare: Transient cortical blindness,visual impairment

Cardiac disorders:
Rare: Arrhythmia (including bradycardia, tachycardia)
Not known: Cardiac failure, cardiac or cardio- respiratory arrest, myocardial infarction, conduction abnormalities, ventricular hypokinesia, coronary artery thrombosis, angina pectoris, spasms of coronary arteries

Vascular disorders:
Uncommon: Flushing
Rare: Hypotension
Very rare: Hypertension, ischaemia
Not known: Arterial spasm, thrombosis, thrombophlebitis, shock

Respiratory, thoracic and mediastinal disorders:
Rare: Cough
Very rare: Dyspnoea
Not known: ~~Non-cardiogenic~~ Ppulmonary oedema, respiratory arrest, respiratory failure

Gastrointestinal disorders:
Uncommon: Nausea, vomiting
Very rare: Abdominal pain/discomfort
Not known: Acute pancreatitis, pancreatitis aggravated, salivary gland enlargement

Skin and subcutaneous system disorders
Uncommon: Rash, pruritus, urticaria
Very rare: angioedema, erythema
Not known: Bullous dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, drug eruption, dermatitis allergic, skin exfoliation

Musculoskeletal and connective tissue disorders:
Very rare: Back pain, muscle spasm
Not known: Arthralgia
Renal and urinary disorders:

Very rare: Impairment of renal function including acute renal failure

General disorders and administration site conditions:
Uncommon: Feeling hot, chest pain
Rare: Pain, discomfort, shivering (chills), pyrexia, administration site reactions including extravasation
Very rare: Feeling cold, asthenic conditions (e.g. malaise, fatigue)

Injury, poisoning and procedural complications:
Not known: Iodism

Intrathecal administration:

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

Meningeal irritation giving photophobia and meningism and frank chemical meningitis have been observed with other non-ionic contrast media. The possibility of an infective meningitis should also be considered. ~~Similarly, manifestations of transient cerebral dysfunction have been seen on very rare occasions with other non-ionic iodinate contrast media. These include seizures, transient confusion or transient motor or sensory dysfunction. Changes in the EEG were noted in a few of the patients.~~

Immune system disorders:
Not known: Hypersensitivity, including anaphylactic/ anaphylactoid reactions

Nervous system disorders:
Uncommon: Headache (may be severe and lasting)
Not known: Dizziness, transient contrast induced encephalopathy (including amnesia, hallucinations, confusion ~~and other neurological symptoms~~)

Gastrointestinal disorders:
Uncommon: Vomiting
Not known: Nausea

Musculoskeletal and connective tissue disorders:
Not known: Muscle spasm

General disorders and administration site conditions:
Not known: Shivering, pain at injection site

Hysterosalpingography (HSG):

Immune system disorders:
Not known: Hypersensitivity

Nervous system disorders:
Common: Headache

Gastrointestinal disorders:
Very common: Abdominal pain
Common: Nausea
Not known: Vomiting

Reproductive system and breast disorders:
Very common: Vaginal haemorrhage

General disorders and administration site conditions:
Common: Pyrexia
Not known: Shivering, injection site reaction

Arthrography:

Immune system disorders:
Not known: Hypersensitivity, including anaphylactic/ anaphylactoid reactions

General disorders and administration site conditions:
Common: Injection site pain
Not known: Shivering

Examination of the GI tract:

Immune system disorders:
Not known: Hypersensitivity, including anaphylactic/ anaphylactoid reactions

Gastrointestinal disorders:
Common: Diarrhoea, abdominal pain, nausea
Uncommon: Vomiting

General disorders and administration site reaction
Not known: Shivering

4.9 Overdose

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 3 days. If needed, haemodialysis may be used to remove iodixanol from the patient's system. There is no specific antidote, treatment of overdose is symptomatic.

Oben angeführte Textabschnitte stellen eine Mindestanforderung dar, zusätzliche nationale Hinweise in diesen Abschnitten sind zu belassen.