**07/2023**

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| **VISIPAQUE 270** | **וידיפאק 270** |
| **VISIPAQUE 320** | **וידיפאק 320** |

**מרכיבים פעילים:**
IODIXANOL 550 MG / 1 ML
IODIXANOL 652 MG / 1 ML

**צורת מינון:**
SOLUTION FOR INJECTION

**רופא/ה, רוקח/ת נכבד/ה,**
חברת אלדן ציוד אלקטרוני בע"מ מבקשת להודיע על עדכון העלון לרופא של התכשיר שבנדון .
העלון עודכן בתאריך מאי 2023 .

**ההתוויה הרשומה לתכשיר בישראל:**
X- ray contrast medium for use in adults for cardioangiography peripheral arteriography (conventional and i.a. DSA) abdominal angiography (i.a. DSA) urography venography and CT-enhancement.
Pediatric use:
cardioangiography urography and CT-enhancement.
Myelography - Lumbar thoracic and cervical myelography

**בהודעה זו מצוינים השינויים המהותיים בלבד.**

**4.4 Special warnings and precautions for use.**

**(…)**

**The use of beta -adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions and reduces the responsiveness of treatment of anaphylactoid reactions with adrenaline.**
**Asthmatic patients are at higher risk on concomitant beta locker therapy (see section 4.5)**
**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.**~~

**(…)**

**Risk for thromboembolism:**
**Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angio-cardiographic procedures with both ionic and non-ionic contrast media. Therefore, meticulous intravascular· administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events.Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended, including close attention to guidewire and catheter manipulation, use of manifold systems· *and/or three-way stopcocks, frequent catheter flushing (e.g. with heparinized saline solutions), and minimizing the length of the procedure. Advanced life support facilities should be readily available***

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~~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 guide wire 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 so as to minimize the risk of procedure-related thrombosis and embolism. .~~

**(…)**

**CNS disturbances**

**Encephalopathy has been reported with the use of iodixanol (see section 4.8).**
**Contrast encephalopathy may manifest with symptoms and signs of neurological dysfunction such as headache, visual disturbance, cortical blindness, confusion, seizures, loss of coordination, hemiparesis, aphasia, unconsciousness, coma and cerebral oedema within minutes to hours after administration of iodixanol, and generally resolves within days. The product should be used with caution in patients with conditions that disrupt the integrity of the blood brain barrier (BBB),**
**Potentially leading to increased permeability of contrast media across the BBB and increasing the risk of encephalopathy**
**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. 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.**
**If contrast encephalopathy is suspected, administration of iodixanol should be discontinued and appropriate medical management should be initiated.**

**(…)**

~~**Normal serum creatinine (<130µ mol/litre)/normal renal function: Administration of metformin should be stopped at the time of administration of contrast medium and should not be resumed for 48 hours and only be restarted if renal function/serum creatinine remains in the normal range.**~~

~~**Abnormal serum creatinine (>130µ mol/litre)/impaired renal function: Metformin should be stopped and the contrast medium examination delayed for 48 hours. Metformin should only be restarted 48 hours later if renal function is not diminished (if serum creatinine is not increased) compared to pre-contrast values.**~~

**(1) Patients with eGFR equal or greater than 60 ml/min/1.73m2 (CKD 1 and 2) can continue to take metformin normally.**

**(2) Patients with eGFR 30-59 ml/min/1.73m2 (CKD 3)**
- **Patients receiving intravenous contrast medium with eGRF equal or greater than 45 ml/min /1.73m2) can continue to take metformin normally**
- **In patients receiving intra-arterial contrast medium, and those receiving intravenous contrast medium with an eGFR between 30 and 44 ml/min/1.73m2 metformin should be discontinued 48 hours before contrast medium and should only be restarted 48 hours after contrast medium if renal function has not deteriorated.**

**(3) In patients with eGFR less than 30 ml/min/1.73m2 (CKD 4 and 5) or with an intercurrent illness causing reduced liver function or hypoxia metformin is contraindicated iodinated contrast media should be avoided.**

**(4)** In emergency cases where renal function is impaired or unknown, the physician should evaluate the risk/benefit of the contrast medium examination, and the following precautions should be

implemented: Metformin should be stopped. It is particularly important that the patient is fully hydrated prior to contrast medium administration and for 24 hours afterwards. Renal function (e.g. serum creatinine), **serum lactic acid and blood pH should be monitored, as well as the patient with regard to signs of lactacidosis.**

**A pH <7.25 or a lactic acid level of >5 mmol/litre are indicative of lactic acidosis. The patient should be observed for symptoms of lactic acidosis. These include vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea and thirst. Metformin should be restarted 48 hours after contrast medium if serum creatinine/eGFR is unchanged from the pre-imaging level.**

**(…)**

**Disturbances in thyroid function**

**Patients with manifest but not yet diagnosed hyperthyroidism, patients with latent hyperthyroidism (e.g., nodular goitre) and patients with functional autonomy (often e.g. elderly patients, especially in regions with iodine deficiency) are at higher risk of acute thyrotoxicosis after use of iodinated contrast media. The additional risk should be evaluated in such patients before use of an iodinated contrast medium. Testing of thyroid function prior to contrast medium administration and/or preventative thyreostatic medication may be considered in patients with suspected hyperthyroidism. The patients at risk of should be monitored for the development of thyrotoxicosis in the weeks following the injection.**
**Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism**
~~**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 goitre may be at risk of developing hyperthyroidism following injection of iodinated contrast media.**~~

**Paediatric population**

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

**(…)**

**Visipaque may, dependent on the indication, contain more than 23 mg sodium per dose. This must be taken into consideration in patients on a controlled sodium diet**

**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. ~~The patient should remain in the hospital environment (but not necessarily the radiology department) for one hour after the last injection, and should return to the radiology department if any symptoms develop~~**

**(…)**

**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 thus tests that measure iodine uptake (using radioactive iodine) will be affected.**

**(…)**

**Asthmatic patients are at higher risk on concomitant beta blocker therapy (see section 4.4).**

**4.6 Fertility, Pregnancy and lactation**

**In neonates who have been exposed to iodinated contrast media in utero, it is recommended to monitor thyroid function (see section 4.4.)**
**~~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.~~**

**(…)**

**Fertility:**
**The effect of VISIPAQUE on human reproduction has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction**

**(…)**

**4.8 Undesirable effects**

**(…)**

**Intravascular administration:**

**Blood and lymphatic system disorders**
**Not known: Thrombocytopenia**

**Immune system disorders:**
**Uncommon: Hypersensitivity**
**Not known: Anaphylactic/anaphylactoid shock, anaphylactoid reaction /anaphylactoid reaction including life-threatening or fatal anaphylaxis, ~~anaphylactoid shock~~;**

Endocrine disorders:
Not known: Hyperthyroidism, hypothyroidism

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

Nervous system disorders:
Uncommon: Headache
Rare: Dizziness, sensory abnormalities including dysgeusia, paraesthesia, parosmia
Very rare: Cerebrovascular accident, amnesia, syncope, tremor (transient) hypoaesthesia sensory ~~abnormalities including taste disturbance, amnesia, paraesthesia, syncope.~~
Not known: Coma, ~~motor dysfunction~~, disturbance in consciousness, convulsion, transient contrast induced encephalopathy* ~~(including hallucination), tremor~~ caused by extravasation of contrast media, which can manifest as sensory, motor or global neurological dysfunction

* See Description of selected adverse reactions for more details.

Eye disorders:
Very rare: Cortical blindness (transient),~~Transient cortical blindness, visual impairment~~ (including diplopia, blurred vision), eyelid oedema

Cardiac disorders:
Rare: Arrhythmia (including bradycardia, tachycardia), myocardial infarction
Very rare: Cardiac arrest, palpitations.
Not known: Cardiac failure, Ventricular hypokinesia, ~~myocardial ischaemia, cardiorespiratory~~ arrest spasm of coronary arteries, cardio-respiratory arrest, conduction abnormalities, coronary artery thrombosis, angina pectoris, ~~spasm of coronary arteries.~~

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

Respiratory, thoracic and mediastinal disorders:
Rare: Cough, sneezing.
Very rare: Dyspnoea, throat irritation, laryngeal oedema.
Not known: Non-cardiogenic Pulmonary oedema, respiratory arrest, respiratory failure bronchospasm, throat tightness, pharyngeal oedema.

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

Skin and subcutaneous system disorders

Uncommon: Rash or drug eruption, pruritus, urticaria
Very rare: angioedema, erythema hyperhidrosis

Not known: Bullous or exfoliative 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:
Uncommon: Acute kidney injury or nephropathy toxic (contrast induced nephropathy-CIN)
Not known: Increased blood creatinine
~~Very rare: Impairment of renal function including acute renal failure~~

General disorders and administration site conditions:
Uncommon: ~~Feeling hot, c~~Chest pain, feeling od body temperature change.
Rare: ~~Pain, discomfort, s~~Shivering (chills), pyrexia, pain and discomfort administration site reactions including extravasation
Very rare: Feeling cold, aAsthenic conditions (e.g. malaise, fatigue), face oedema, localised oedema
Not known: Swelling

(…)

Intrathecal administration:

(…)

Nervous system disorders:
Uncommon: Headache (may be severe and lasting)
Not known: Coma, disturbance in consciousness, convulsion, transient contrast-induced encephalopathy* caused by extravasation of contrast media, which can manifest as sensory, motor or global neurological dysfunction
Dizziness, transient contrast induced encephalopathy (including amnesia, hallucinations, confusion)

(…)

Description of selected adverse reactions:
Transient contrast-induced encephalopathy:
In unknown occasions the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex that may cause contrast-induced encephalopathy The symptoms may include agitation, transient cortical blindness, amnesia, hallucination, paralysis, paresis, disorientation, transient speech disorder, aphasia, dysarthria.

**<u>מקראה לעדכונים המסומנים:</u>**
מידע שהוסר - מסומן בקו אדום חוצה ~~XXX~~
תוספת - כתב **כחול**

**<u>עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא:</u>**

קיימים עדכונים נוספים . למידע נוסף יש לעיין בעלון לרופא המעודכן.

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| העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות , וניתן לקבלו מודפס על ידי פניה לבעל הרישום אלדן ציוד אלקטרוני בע"מ, בנין ניאופרם, רח' השילוח 6 ת.ד 7641 פתח תקוה 4917001, טלפון: 03-9371111, פקס: 03-9371100. |

בברכה,

עוז וולך

רוקח ממונה