SUMMARY OF PRODUCT CHARCTERISTICS

1. NAME OF MEDICINAL PRODUCT

PAMİRAY 370 vial for injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

1 ml solution contains 755,2 mg iopamidol equivalents to 370 mg iodine.

Excipient(s):
Disodium calcium edetate (0,39 mg). For excipients, refer to 6.1.

3. PHARMACEUTICAL FORM

Injectable solution
Clear, colorless or light yellow solution, free from visual particulates.

4. CLINICAL PROPERTIES

4.1. Therapeutic indications

Non-ionic radiographic contrast substance which dissolves in water for only diagnostis purposes.

Neuroradiology
- Myeloradiculography
- Cysternography,
- Ventriculography

Angiography
- Cerebral arteriography
- Coroner arteriography
- Thorasic aortography
- Abdominal aortography
- Angiocardiogarphy
- Selective vicceral arteriography
- Peripheral arteriography
- Venography

Digital substraction angiography (DSA)
- DSA for cerebral arterias,
- DSA for peripheric arterias,
- DSA for abdominal arterias.

Urography
- İntravenous urography

Other indications
- Contrast increasing in BT,
- Artrography
- Phystulography
- Hysterosalpingography

4.2. Posology and administration route

Posology/ administration frequaent and time: Dosage and administration rate can change depends on administration route, clinical problem, technic, monitoring area, equipments as well as age, body weight and conditions of patients (renal funtion, cardiac function, etc.). Dosages are described with volume (ml), each kilogram (kg), each injection or kilogram body weight for especially pediatrics. Most lowest and effective dosage must be given.

Neuroradyology

	Concentration (mg I/ml)	Recommended dosage (ml)
Myeloradiculograpgy	300	5-15
Cysternography and ventriculography	300	3-15

Angiography

	Concentration (mg I/ml)	Recommended dosage (ml)
Cerebral arteriography	300	5-10 for each bolus
Coroner arteriography	370	8-15 for each bolus
Angiocardiography	370	1,0-1,2/kg
Thorasic aortography	370	1,0-1,2/kg
Abdominal aortography	370	1,0-1,2/kg
Selective vicceral arteriography	300-370	Depends on vascular area to be examined.
Peripheric arteriography	300-370	40-50
Digital substraction angiogaphy	370	Depends on vascular area to be examined.
Venography (flebography)	300	30-50

Ürography

Recommended dosage for this type examination is 30-50 ml for adults. Osmotic-diuresis occurring with non-ionic agents results in suitability of PAMİRAY for newborns and patients with light or middle degreed renal insufficiencies. This new contrast substance provides usefull nephrography diagnosis in patients with majör renal insufficiency.

Other diagnostic processes

	Concentration (mg I/ml)	Recommended dosage (ml)
Increasing contrast for BTscanning	300-370	0,5-2/kg
Artrography	300	
Phystulography	300	
Hysterosalpingography	300-370	5-20

For increasing contrast in BT scanning, PAMİRAY must inject by intravenous route as bolus or drop infusion or combination of these two methods.
While administration of infusion is restricted by old generation BT equipments, bolus administration is recommended for spiral BT and new multislice (multiple sections) BT scoping contrast incresing in arterial phases.
While infusion recommends for slow equipments, bolus injection is recommended for rapid equipments. Like histerosalpingography, artrography and phystulography, total dosage to be injected depends on age and body weight of patient and clinical conditions.

Administration route: Solution of contrast substance for intravscular and intratecheal usage must heat until body temperature.
Before using, examine product regarding to be sure for damages on cap and closure.
Contrast solution must withdraw under aseptic conditions with sterile syringes. Intravascular or intratecheal administration with or without catheters and canulles must conduct under maximum aseptic conditions. Vial must use immediately after first opening. Discard of unused contrast substances.
In case of repeatable usage for equipments, special precautions must be given to be sure of residual purifier and residual contamination. Like other contrast substances with iodine, PAMİRAY can interact with metallic surface containing copper (example; brass) and so, contrast substance must not use with equipments containing copper.

Additional information regarding to special populations
Renal insufficiency: Refer to **"Posology/administration route and time"** section under head of **"Urography"** .
Renal insufficieny: There is no special condition regarding to usage in patients with liver insufficieny.
Pediatric population: PAMİRAY 300 injectable solution is recommended especially for pediatric urography in newborns and patients with renal insufficiency.
Geriatric population: Dosage arrengement does not require.

4.3. Contrendications
• Hypersensivity to active ingredient, water soluble contrast substance, iodine or other excipients,

- Intratecheal administration: Intratecheal administration of iopamidol with corticosteroids is contrendicated. **(**refer to **"4.5. Interaction with other medicines and other interaction types"**).
- Because of over dosage risks, repetition of immedient myelography is contrendicated in technical inadequacy.
- Hysterosalpingography: Evaluation of women's genital system is contrendicated for pregnant women, bearing pregnant women or acute inflamations **(**refer to **"4.6. Pregnancy and lactation"**).

4.4. Special precautions fand warnings for usage

Crystallation can occur rarely in iopamidol solutions. Reasons of these phenomen are damaged or broken vials. So, product must not use.

Usage of contrast substance is restricted to exactly indicated cases for diagnosis.

Usage of contrast substance in cardioangiography must perform only in hospital or intense care units with enough eqipments by authorised personel.

In other routine diagnosis by contrast substance, required medcines and equipments must availible for recucitation in radiology department (ambu baloon, oxygen tubes, antihystaminics, vasopressor medicines, cortisone).

PAMİRAY contains less than 1 mmol sodium in each dosage (23 mg). We accepted that product does not contain sodium.

Usage in special populations

Newborns, children

Especially newborns (age < 1 year) are sensitive to electrolit unbalancing and hemodynamic changes. Special care must be given to be using dosage, details of procedure and patient conditions.

Geriatrics

Especially when higher dosages are needed and in geriatrics are under special risk group with regarding to reactions occuring because of decreasing physical functions. In these patients, occuring possibilities of myocard ischemias, majör arytmias and prematüre ventricular complexesare more higher. Possibility of acute renal insufficiency is much higher in these patients.

Womens with child bearing potential

In womens with child bearing potential, suitable examinations must perform and precautions must taken during any tests with or without contrast substance.

Conditions results in increasing serious advers effects

In following conditions, careful risk/benefit evaluation must perform before administration of product because of increasing risks of advers events. Patients under risk of advers events are patients with allergy history (broncial asthma, hay fever, food allergy) or suspicious reactions showed in the past to contrast substance or iodine.

Patients waldenström paraproteinemia, multiple myeloma or serious renal or liver function insufficiencies are under higher risk group. In these cases, enough hidratation is recommended after administration of contrast substance. Radiological examination of patients with hyperthreoditis, must perform until clearly needed.

In case of tiroid tests by radioactive labelled iodine, iodine uptake will decrease for 1-2 days or two weeks after dosage of contrast substance with iodine eliminated by renally.

Renal function disabilities can trigger acute renal disfunction after administration of contrast substance. Preventative measurements are: Determination of high risk grouped patients, enough hidratation must provided before administration of contrast substance and IV infusion and during procrdure until clearence of contrast substance, nephrotoxic medicines must not given, majör operation and renal angioplasty must not perform until clearance of contrast substance, examinations with new contrast substance must postpone until returning of renal functions to past conditions.

Patients under dialyses, removable contrast substance like PAMİRAY can use.

Before administration of hypertonic contrast solution liquid intake must restrict and arrange liquid-electrolite inbalance. Water intake must not restricted in newborns and children and liquid –electrolite inbalance must corrected before administration of hypertonic contrast substance.

Diabetic patients with renal damage is factor providing acute renal insufficiency after administration of intravascular contrast substance. Lactic asidosis can be rapid in patients using biguanids. **(**Refer to **"4.5. Interactions with other medicines and other interaction types"** section).

When contrast substance is injected by intravenous or intraarterial, oracletation may increase in homozigot person for oracle cell disease. Enough hidratation is recommended.

Administration in patients with pheocromasitona, heavy hypertansive crisis can occur during administration of contrast substance (rarely out of control).

Administration of contrast substance with iodine execarbate symptoms of myestania gravis. Like other contrast substance, risks of neurologic complications are more higher in patients with symptomatic cerebrovascular disease, new arrest, transient ischemic attack, chronic intracranial hemorragy and changing permeability of blood-brain barrier, cerebral oedema, acute demyelenisation, epilepsy history.

Neuroradyology

In case of spinal liquid blockage, contrast substance must remove as soon as possible.

Patients with convulsions, anticonvulsane treatment must continue before radiologic procedure and after these procedures.

In case of occuring convulsive crisis during procedure, administration of intravenous diazepam or phenobarbital are recommended.

Intratecheal administration

Risk/benefit ratio must evaluate carefully in case of epilepsy history before clinic anamnesis orblood is avalible in cerebrospinal liquid or local –systemic infections with bacteriaemia possibilities.

Administrator must evaluate diagnostic requirement for patient in these type cases.

After completing direct servical or lumbo-cervical procedure:

- Head of table must stand up (45^0 angle) for two minutes, so contrast substance goes to caudal end.
- Patients must avoid heavy and especially active movements during first hours. Close monitoring of patients must require, patient must calm and at stand up position of his head in his bed.
- If possible patient must take liquids by orally and eat meal.

Angiography

Risks related to this special evaluation can increase with advanced arteriosclerosis and hypertension.

In patients to be performed angiocardiographic procedure, special care must given to right heart and pulmonary circulation. Insufficiency of right heart and pulmonary hypertension can accelerate bradicardia and systemic hypotension during injection of organic iodine solution.

When contrast substance injects into cardiac rooms, special care must be given to cyanotic newborns with cardiac function abnormality and pulmonary hypertansion.
In patients with congestive cardiac insufficiency, special care must be given to potential increasing of circulatory osmotic loading because of accelerating pulmonary oedema during injection.
In evaluations of aortic cavity, catheter extremity must be inserted carefully to prevent CNS damage, bradicardia, hypotension depending on over pressure transmitting to braciosephalic branch of aorta.
Intraarterial injections of contrast substance may cause vasospasm and cerebral ischemic phenomanias.
Over pressure transmitting with injector pump in abdominal angiography can cause necrosis, intestinal infarctus, retroperitoneal bleeding, lessions in spinal ducts, renal infractus.
Administration of PAMİRAY 370 mg/ml injectable solution in patients to be performed peripheric angiography can cause non-appearant pain with 300 mg/ml concentration.
In vitro showed that inhibitory effects of non-ionic contrast substance on hemoastatis mechanism is more lower than ionic contrast substance with same concentration.
Because of this, sensitive angiographic techniques like close monitoring of canules and catheters, usage of three sided valve and distrubution systems, frequent cleaning of catheters with heparined serum physiologics, decreasing of procedure timing.

4.5. Interactions with other medicines and other interaction types

Diabetic patients treating with biguanid class oral antidiabetics, biguanids must stop for 48 hours after administration of contrast substance to prevent lactic asidosis and re-start after showing renal functions returning to previous values **(**refer to **"4.4. Precautions and warnings for special usage"** section).
In cardiac or/and hypertansive patients under treatment with diuretics, ACE inhibitors, beta blocker agents, risks of advesr events are much higher during administration of contrast substance with iodine.
In patients under treatment with immunomodulators like interleucins-2 and interpherons, allegy type reactions are seen more frequently and these show late type reactions.

Intratecheal administration
Intratecheal administration of iopamidol with corticosteroids are contrendicated. Patients with knowing convulsive disease, anticonvulsane treatment continue before myelographic procedures and after these procedures. Because of decreasing sencop threshold, neuroleptics must avoided. These conditions are valid for also analgesics, antiemetics, antihistaminics or sedative medicines which in phenotiazin group. When it is possible, treatment with these medicines must stop before minimum 48 hours from radiologic analysis and treatment must srat after 24 hours.
Alcoholism or drug dependence increase permeability of blood-brain barrier. This is resulted in CNS disfunctions by facilitating penetration of iodine agents to brain tissues. Special care must given to possible decreasing of sencop threshold.

Additional information related to special population: Interaction studies related to special population are not performed.
Pediatric population: Interaction study related to pediatric population is not conducted.

4.6. Pregnancy and lactation

General recommendation
Pregnancy category is B.

Womens with child bearing potential/ Contraception
In patients with child bearing potential suitable evaluations must perform and precautions must taken during any tests with x-rays with or without contrast substance.

Pregnancy period
Clinical data related to pregnant women administered iopamidol are not availible. Animal studies are not shown any demonstrations related to damages on feuts/embryo or fertility disfunctions. Special care must given to pregnant women when contrast substance is prescribed.
Histerosalpingography: Analysis of women genital system is contrendicated in pregnant women, child bearing women and acute inflamation **(**refer to **"4.3. Contrendications"** section).

Lactation period
It is not known whether iopamidol excreted to human milk or not. In spite of there was not informed serious advers events in newborns, special care must given when iopamidol is aministered to lactating women because most of injectabl contrast substances enter to mother milk.

Reproducing abilities/ Fertility
Animal studies are not shown any demonstrations related to damages on feutus/embryo or fertility disfunctions.

4.7. Effects on driving and using machinery
There is not known effects on driving and using machinery. Furtermore, is is recommended that driving and using machinary must avoided for 1 hour later from last injection becauseof early reaction risks.

4.8. Side Effects
Usage of iodine compounds causes unexpected side effects. Advers reaction against iopamidol can occur approximately 0,7 patienys per billion. These side effects are generally mild or low degree; but rarely these may be serious or can cause death.
Symptoms are nausea, vomiting, headache, fever or rinitis. Immedient medical care can require for more serious side effects related to cardiovascular side effects like vasodilatation with appearant hypotension, tachicardia, dispne, agitation, sianosis, memory loss. In most cases advesr event occur within 1-2 minutes after administration. Furtermore, late type reactions like cutenous reactions may occur after 7 days or after 2-3 days from administration.

<u>Anaphylaxi</u>
Anaphylactic reactions/hypersensivity can seen for followings: light localise or more diffused angioneuratical oedema, oedema in tongue, laryngospasm or larynx oedema, dysphasia, pharengitis and narrowing in throat, pharingolaryngeal pain cough, conjuctivitis, rinitis, sneezing, hot flushes, astenia, dizziness, pale face dispnea, wheezing, broncospasm and mild hypotension. Skin reactions can occur like different type urticaria, common erytema, common blister, urticaria or pruritis. Independent from administered dosage and administration route occuring these side effects may be representative symptoms of shock. In these cases, administration of contrast substance must stop and specific treatment should initiate by venous route.
Emergent treatment can require for serious reactions related to cardiovascular system like vasodilatation with appearant hypotension, tachicardia, dispnea, agitation, sianosis and sencop.Pain and swelling at injection site can occur. In rare cases, penetrating of contrast substance to exrta vascular area may cause inflamation, scin necrosis and compartman syndrome.
Serious skin pathology:

Like other contrast substances with iodine, rarely mucocutanous syndroms like Stevens-johnson syndrome, toxic epidermal necrosis (Lyell syndrome) and erytem multiforme were informed after iopamidol administration. Addition to mentioned side effects above, there are more specific advers events for different administration routes in stated at below table.
Very common (> 1/10); common (> 1/100- < 1/10); non-common (> 1/1.000 -< 1/100); rare (> 1/10.000- < 1/1.000); very rare (< 1/10.000), not known (can not predict from availible data).

İntravascular administration

System organ class	**Very rare (<1/10.000)**	**Isolated cases**
Blood and lenphoidic system disease	Trombocytopenia	
Metabolism and nutrition disorders	Anorexia, asidosis	
Psychiatric disorders	Confusion	
Nervous system disorders	Headache, vasovagal sencop, transitient ischemic attack, amnesia, suspected memory level or memory loss, coma, paraestesia, dizziness, pralysis, tremor, convulsion, involuntary muscle contractions, somnelance, disturbance in tasting behaviour	Parestesia
Eye disorders	Vision defeating, increasing lacrimal liquids, pruritis in eyes, conjuctivitis, photophobia, transitient blindness	
Ear and labyrinth disorders	Earing defects	Transitient progresive deafness
Cardiac disorders	Tachycardia, bradicardia, myocard ischemia orinfractus, cardiac insufficiency, angina pectoris, cardiac-breathing arrest, sianosis. Cardiac rytm defects like ventricular bigemini, extracystoller, atrial fibrilation, ventricular tachycardia, ventricular fibrilation can occur generally after procedures of cardiac angiographic and coroner catheteterisation.	
Vascular disorders	Hemodynamical changes like hypotension, hypertension, circulation collaps, thrombophlebitis, arterial spasm, skin pruritis, vasodilatation, thromboembolism and paling	Arterial thrombosis, phlebotrombosis

Respiratuvary, thorasic and mediastinal disorders	Dyspne, breathing diffuculties, asthma, apnea, narroving in throats, cough, breathing congestion, sneezing, rinitis, defects on breathing rytm, pumonary oedema, layrnx oedema, cardiac arrest, cardiac insufficieny, acute breathing insufficiecy syndrome	
Gastrointestinal disorders	Nausea, vomiting, severe disgusting, abdominal pain, excessive or low salvation, increasing of salvation gland	
Skin and subkutanous tissue disorders	Increasing of sweeting, urticaria, pruritis, pheriorbital oedema, skin oedema	
Muscle- skeleton system and ligament tissue disorders	Back pain, muscle spasm, muscle pain, muscle cramps, muscle insufficiency	
Renal any urinary disorders	Transitient renal insufficiency, acute renal insufficiency, anuria, oligouria, urinary incontinance, pain in urinary system, hematuria	Urinary retention
General disorders and injection site disorders	Increasing fever, shivering, fatigue, general pain, chest pain, feeling difficulty in chest, hot flushes or feeling cold Injection site reactions are characterised by injection pain or/and erytema and/or swelling.	
Investigations	Increasing of ventricular preload, ST segmental depresion, changes in electrocardiogram, abnormal electrocardiogram, increasing T vave amphludid in electrocardiogram, decresing cystolic blood pressure, transitient defeats in renal function tests, abnormal blood electrolits	QTprolonging in electrocardiogram
Injuring, poisoning and procedural complications	As a result of procedure, coroner arter sissection and periferic embolism may occur.	Following axillary arter ponction damages on bracial plexus. As a reslt of procedural damage, vascular psudoanevrism is informed.

Intratecheal administration

Because of administration route, side effects after myelography are result in slow absorbtion from injection site and distrubution to all body after 1-2 hours later from administration. Recations generally can occur within 24 hours later from injection. Advers events are informed at below table.

System organ class	**Very rare (<1/10.000)**	**Isolated cases**

Infections and enfestations	Aseptic menengitis As a result of procedurel damage, bacterial menengitis is seen.	
Metabolism and nutrition disorders	Acidosis	
Psyciatric disorders	Confusion, orientation disorders, hallucination, depersonalisation, anxiety, depression, uneasiness, ecolali, agitation, transitient psycosis	Emotional distress
Nervous system disorders	Dizziness, headache, suspensed memory level or memory loss, sencope, hypoasthesia, pareastesia, servical root pain, menengisim, radiculit, amnesia, somnalence, burning feel, Guillain-Barre syndrome, nervous system disfunctions, ataxia, paralysis, convulsion, hypertoni, hypotoni, tremor, disphagia, myelitis, involuntary muscle contractions, muscle spasitiy, sensorymotor disfunction, radiculopaty or cauda equina syndrome, periferic neuropathy.	
Eye disorders	Extraocular muscle disfunctions, incresing lacrimation, pruritis in eyes, conjuctivitis, photophobia	Transitient vision disfunctions
Eye and labyrinth disorders	Transitient progressive deafness, hearing disfunctions	Tinnitus
Cardiac disorders	Tachicardia, sianosis	Aritmias
Vascular disordres	Skin flushes, hypertension, periferic coldness	
Respiratory, torasic and mediastinal disorders	Dispnea, stooping inhalataion, breating arrest	Apnea
Gastrointestinal disorders	Nausea, vomiting	Diarrea
Skin and subcutanous tissue disorders	Increasing sweeting	
Muscle-iskeleton system and connective tissue disorders	Backpain, muscle-iskeleton system pain, muscle cramp, pain at extremities	Muscle weakness
Renal and urinary disorders	Acute renal insufficieny, urinary retention, urinary incontinance	Renal insufficiency, oligori, hematuria
General disorders and injection site reactions	Weakness, tiredness, shivering, incresing fever, irritability	
Investigations	Abnormal blood electrolits	Transitient defeats in renal function tests

Urography
Informed reactions at intravenous urogrophy are expalined at top of the section.

Other tests
Informed reaction at artrography and phystilography cases are generally shown irritative symptoms added to availible tissue inflamation. During histerosalpingography, vaso-vagal reactions may occur.

4.9. Over dsoages and treatment
There is no any informed cases related to over dosages.
Most of advers events **(**refer to **"4.8. Side effects"** section) do not depend on dosage and because of this medical care are needed like mentioned in **"4.4. Special usage precautions and warnings"** section.
In case of wrongly administered dosage, hidratation of patient must be enough to facilititate elimination of dosage by renally.
In renal disfuction cases occured in the past or after administration of contrast substance, hemodialysis must perform for elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties
Pharmacotherapeutic group: non-ionic radiographic contrast substance with low osmalarity.
ATC code: V08AB04
Iopamidol is radioopac substance soluble in water. It has low toxicity and there is no teratogenic effects.
Results of studies in dogs are showed that iopamidol at two or four times higher from administration dosage for clinical usage can cause light hypertension and incresing breathing numbers following transitient bradicardia and hypotension. These effects are reversed to normal after 2-4 minutes from stopping treatment.
Results of prospective study with Multislice BTare showed that nephropathy incidence was very low at dosage equivalents to 40 g iodine in patients with mild or heavy renal disfunction (creatinin clerance was between 10-59 ml/minute/1,73 m^2) after intravenous administration and BT analysis and also there were no any differences between non-ionic isoosmolar dimer and non-ionic monomer iopamidol with low osmolality.
Serum creatinin was equivalent to 0,5 mg/dl or was not more much higher with iopamidol. In 3,9%-4,0 patients treated with iopamidol or non-ionic dimer showed 25% or more much higher incresing of creatinin clerence according to basal values.
In patients analysed by cardioangiographic tests with iopamidol, nephropathy incidency related to contrast substance were seen similar to incidence seen after non-ionic isoosmolar dimer.

5.2. Pharmacokinetic properties
Metabolism: Iopamidol is not metabolism in animals and humans much more.
After iopamidol injection, elimination is mainly by renally. In dogs, 93%-95 of dosage is elininated by renally, 0,5% is eliminated by ballast within 7-10 hours. More than 90% administered dosage for humans is eliminated by renally within 24 hours. In eliminatin stage half life of blood level is approximately 60 minutes in dogs and 90-120 minutes in humans. After intratecheal administration steadt state plasma level can obtain within 90-150minutes and total elimination occur within 24 hours.

5.3. Pre-clinic safety data
According to convensional investigations conducted related to pre-clinical data, human pharmacology, genotoxicity and reproductive toxicity, there is no special risk.

6.PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Trometamol (Tromethamine)
Disodium calcium edetate
Diluted hydrochloric acid
Water for injections

6.2 Incompabilities
Do not mix with other contrast substances except for heparin.

6.3 Shelf life
36 months

6.4 Precautions for storage
Protect from strong light. Store at below 25 °C.

6.5 Nature and contents of packaking
Type 1 according to European Pharmacopea, 50, 100 and 200 ml, one glass vial containing injectable solution with bromobuthyl rubber closure.

6.6 Discarding of remaining parts ofmedicines and precautions for discarding

Unused products or discarding materials must discard suitable procedures according to "Guideline on medicinal garbage" and "Control guideline on packaging and packaging garbage".

7. REGISTRATION HOLDER

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8. REGISTRATION NUMBER(S)

241/70

9. FIRST REGISTRATION DATE/RENEWAL DATE

First registration date: 02.04.2012

Renewal date:

10. REVISION OF SMPC