

COOK®

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November 17, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Citizen Petition, Docket Number 00P-1452/CP 1

Dear Sir or Madam:

As requested in a telephone conversation with Emily Thomas, Office of Generic Drugs, a revised statement of grounds, draft Iopamidol-M Injection labeling and reference drug labeling have been provided. At this time, Cook Imaging Corporation requests that the additional information be incorporated into the original Citizen Petition, Docket Number 00P-1452/CP 1.

If you have any questions or require additional information, please call me at 800.353.0887.

Sincerely,



Kelly Davis
Regulatory Affairs Associate

00P-1452

SUPI

November 17, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Citizen Petition

B. Statement of Grounds

Iopamidol-M Injection is a diagnostic, non-ionic radiopaque contrast media for intrathecal administration. Cook Imaging intends to manufacture Iopamidol-M Injection, 200 and 300 mgI/mL strengths, in a 20 mL syringe.

Currently, Cook Imaging manufactures Iopamidol Injection, 200, 250, 300 and 370 mgI/mL strengths, in 50 mL, 100 mL and 200 mL vials. Iopamidol Injection and Iopamidol-M Injection have identical formulation processes as well as finished product release specifications.

The 20 mL syringe is composed of the same USP Type I borosilicate glass as the approved 50, 100 and 200 mL vials. The 20 mL syringe will use the currently approved 4405/50 gray butyl stopper.

Cook Imaging has obtained 25 months stability (Upright/Inverted) at 25° to 30°C and 40°C/75% RH for the Iopamidol-M Injection 20 mL syringe.

The stability data follows the same profile as the currently approved 50, 100 and 200 mL vial sizes (ANDA No. 74-881):

1. No out of specification results were observed in the Iopamidol-M Injection, 200 and 300 mgI/mL, stability data. Similar stability trends were observed between Iopamidol-M Injection, 200 and 300 mgI/mL, and Iopamidol Injection, 200 and 300 mgI/mL.
2. No stability lot of Iopamidol-M Injection in either dosage form has shown evidence of instability in the form of degradation or pH shift.

Draft Iopamidol-M Injection Labeling

Iopamidol-M Injection, 200 mgI/mL, Syringe Label

COOK IMAGING
COOK IMAGING

RETAIN IN CARTON
UNTIL TIME OF USE

15 mL

NDC 58707-007-13

20% Organically Bound Iodine Rx only

IOPAMIDOL-M 200

Iopamidol Injection USP, 41%

SEE INSERT FOR
INDICATIONS AND
DOSAGE INFORMATION

For Intrathecal Use

Each mL of sterile, nonpyrogenic, aqueous solution provides 408 mg Iopamidol with 1 mg tromethamine and 0.25 mg edetate calcium disodium, pH adjusted to 6.5-7.5 with hydrochloric acid. Each mL contains approx. 0.029 mg (0.001 mEq) sodium and 200 mg organically bound iodine.

Check for particulate matter and discoloration prior to administration. Iopamidol solutions should be used only if clear and within the normal colorless to pale yellow range.

Single Dose Syringe • Discard unused portion • Protect from light • Store at room temperature not exceeding 30°C (86°F)

Cook Imaging Corporation, Bloomington, Indiana 47403 Made in U.S.A. 3-122-853
Distributed by Cook Incorporated, Bloomington, Indiana 47402 1-800-457-4500

Approx. Vol., cc
4 6 8 10 12 14

Iopamidol-M Injection, 300 mgI/mL, Syringe Label

COOK IMAGING
COOK IMAGING

RETAIN IN CARTON
UNTIL TIME OF USE

15 mL

NDC 58707-005-13

Rx only

SEE INSERT FOR
INDICATIONS AND
DOSAGE INFORMATION

For Intrathecal Use

Each mL of sterile, nonpyrogenic, aqueous solution provides 612 mg Iopamidol with 1 mg tromethamine and 0.39 mg edetate calcium disodium, pH adjusted to 6.5-7.5 with hydrochloric acid. Each mL contains approx. 0.043 mg (0.002 mEq) sodium and 300 mg organically bound iodine.

Check for particulate matter and discoloration prior to administration. Iopamidol solutions should be used only if clear and within the normal colorless to pale yellow range.

Single Dose Syringe • Discard unused portion • Protect from light • Store at room temperature not exceeding 30°C (86°F)

Cook Imaging Corporation, Bloomington, Indiana 47403 Made in U.S.A. 3-123-853
Distributed by Cook Incorporated, Bloomington, Indiana 47402 1-800-457-4500

Approx. Vol., cc
4 6 8 10 12 14

Iopamidol-M Injection, 200 mgI/mL, Box Label

15 mL single use syringe NDC 58707-007-13 10 syringes
STERILE AQUEOUS INJECTION

20% Organically Bound Iodine
IOPAMIDOL-M 200
Iopamidol Injection USP, 41%

For Intrathecal Use
Each mL of sterile, nonpyrogenic, aqueous solution provides 408 mg Iopamidol with 1 mg tromethamine and 0.26 mg edetate calcium disodium, pH adjusted to 6.5-7.5 with hydrochloric acid. Each mL contains approx. 0.029 mg (0.001 mEq) sodium and 200 mg organically bound iodine. See insert for indications and dosage information. Check for particulate matter and discoloration prior to administration. Iopamidol solutions should be used only if clear and within the normal colorless to pale yellow range. Single dose syringe. Discard unused portion. **Protect from light. Store at room temperature not exceeding 30°C (86°F). RETAIN SYRINGES IN CARTON UNTIL TIME OF USE.**
Rx only

COOK IMAGING
COOK PHARMACEUTICALS

Cook Imaging Corporation, Bloomington, Indiana 47403 Made in U.S.A.
Distributed by Cook* Incorporated, Bloomington, Indiana 47402 1-800-457-4500



3-127-853 +H8350071321

Iopamidol-M Injection, 300 mgI/mL, Box Label

15 mL single use syringe NDC 58707-005-13 10 syringes
STERILE AQUEOUS INJECTION

30% Organically Bound Iodine
IOPAMIDOL-M 300
Iopamidol Injection USP, 61%

For Intrathecal Use
Each mL of sterile, nonpyrogenic, aqueous solution provides 612 mg Iopamidol with 1 mg tromethamine and 0.39 mg edetate calcium disodium, pH adjusted to 6.5-7.5 with hydrochloric acid. Each mL contains approx. 0.043 mg (0.002 mEq) sodium and 300 mg organically bound iodine. See insert for indications and dosage information. Check for particulate matter and discoloration prior to administration. Iopamidol solutions should be used only if clear and within the normal colorless to pale yellow range. Single dose syringe. Discard unused portion. **Protect from light. Store at room temperature not exceeding 30°C (86°F). RETAIN SYRINGES IN CARTON UNTIL TIME OF USE.**
Rx only

COOK IMAGING
COOK PHARMACEUTICALS

Cook Imaging Corporation, Bloomington, Indiana 47403 Made in U.S.A.
Distributed by Cook* Incorporated, Bloomington, Indiana 47402 1-800-457-4500



3-128-853 +H8350051321

Iopamidol-M Injection Nursing Notice

NURSING NOTICE

This patient has had a myelogram using IOPAMIDOL-M, a nonionic water-soluble contrast media. Patient management is *different from* myelograms using *oily media*.

- Raise head of stretcher to at least 30° before moving patient onto it.
- Movement onto stretcher, and off the stretcher to bed, should be done slowly with patient completely passive, maintaining *head up* position.
- Before moving patient onto bed, raise head of bed 30° to 45° and maintain the patient in this position under close observation for 12 to 24 hours.
- Advise patient to remain still in bed, in *head up* position for the first 24 hours.
- Obtain visitors cooperation in keeping the patient quiet and in *head up* position, especially in first few hours.
- Encourage oral fluids and diet as tolerated.
- Antinauseants of the phenothiazine class should *not* be administered to treat postprocedural nausea or vomiting.
- Persistent nausea and vomiting may cause dehydration and should be reported promptly; request consideration for IV fluids.
- For questions or special instructions call: 1-800-457-4500

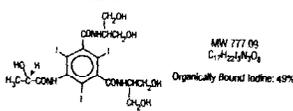
03-124-853

Iopamidol-M Injection Package Insert

The pH of IOPAMIDOL-M contrast media has been adjusted to 6.5-7.5 with hydrochloric acid and/or sodium hydroxide. Perinent physicochemical data are listed below. IOPAMIDOL-M (Iopamidol injection) is hypertonic as compared to plasma and cerebrospinal fluid (approximately 285 and 301 mOsm/kg water, respectively).

Parameter	Iopamidol	
	41%	61%
Concentration (mg/mL)	200	300
Osmolality @ 37°C (mOsm/kg water)	413	616
Viscosity (cP) @ 37°C	2.0	4.7
@ 20°C	3.3	8.8
Specific Gravity @ 37°C	1.227	1.339

Iopamidol is designated chemically as (S)-N,N'-bis(2-hydroxy-1-(hydroxymethyl)-ethyl)-2,4,6-triiodo-5-iodaminoethylamide. The structural formula is:



CLINICAL PHARMACOLOGY
The pharmacokinetics of intravenously administered Iopamidol in normal subjects conform to an open two-compartment model with first order elimination (a rapid alpha phase for drug distribution and a slow beta phase for drug elimination). The elimination half-life in plasma is approximately two hours, the half-life is not dose dependent. No significant metabolism, degradation, or biotransformation occurs.

Iopamidol is rapidly absorbed into the bloodstream from cerebrospinal fluid (CSF), following intrathecal administration. Iopamidol appears in plasma within one hour and virtually all of the drug reaches the systemic circulation within 24 hours. Iopamidol is excreted mainly through the kidneys following intrathecal administration, and the drug is essentially undetectable in the plasma 48 hours later. In patients with impaired renal function, the elimination half-life is prolonged dependent upon the degree of impairment. In the absence of renal dysfunction, the cumulative urinary excretion for Iopamidol, expressed as a percentage of administered intravenous dose, is approximately 35 to 40 percent at 60 minutes, 80 to 90 percent at 8 hours, and 90 percent or more in the 72- to 96-hour period after administration. In normal subjects, approximately 1 percent or less of the administered dose appears in cumulative 72- to 96-hour fecal specimens.

Iopamidol displays little tendency to bind to serum or plasma proteins.
No evidence of *in vivo* complement activation has been found in normal subjects.
Animal studies indicate that Iopamidol does not cross the blood-brain barrier to any significant extent following intravascular administration.

INDICATIONS AND USAGE
IOPAMIDOL-M (Iopamidol injection) is indicated for intrathecal administration in adult neurodiagnostic imaging myelography (lumbar, thoracic, cervical, total columnar), and for contrast enhancement of computed tomographic (CT) osteomyelography and ventriculography. IOPAMIDOL-M 200 (Iopamidol injection USP, 41%) is indicated for thoracic-lumbar myelography in children over the age of two years.

CONTRAINDICATIONS
Intrathecal administration of corticosteroids with Iopamidol is contraindicated. Because of overdose considerations, immediate repeat myelography in the event of technical failure is contraindicated. (See interval recommendation under DOSAGE AND ADMINISTRATION.) Myelography should not be performed in the presence of significant local or systemic infection where bacteremia is likely.

WARNINGS
The need for myelographic examination should be carefully evaluated. Iopamidol should be administered with caution in patients with increased intracranial pressure or suspicion of intracranial tumor, abscess or hematoma, those with a history of convulsive disorder,

severe cardiovascular disease, chronic alcoholism, or multiple sclerosis, and elderly patients. Particular attention must be given to state of hydration, concentration of medium, dose, and technique used in these patients.

Contrast media may promote sepsis in individuals who are homozygous for sickle cell disease when injected intrathecally or intratranally. Although Iopamidol-M is not injected intravascularly, measurable plasma levels are attained after intrathecal administration. If a very bloody cerebrospinal fluid is observed, the possible benefits of myelographic examination should be considered in terms of risk to the patient.

Patient on anticonvulsant medication should be maintained on this therapy.
Direct intracerebral or ventricular administration for standard radiography (without computerized tomographic enhancement) is not recommended. Inadvertent intracerebral entry of a large or concentrated bolus of the contrast medium, which increases the risk of neurotoxicity, can be prevented by careful patient management. Also, effort should be directed to avoid rapid dispersion of the medium causing inadvertent use of intracranial levels (e.g., by active patient movement). If such intracerebral entry of the medium occurs, prophylactic anticonvulsant treatment with diazepam or barbiturates orally for 24 to 48 hours should be considered.

Use of medications that may lower the seizure threshold (phenothiazine derivatives, including those used for their antihistaminic properties; tricyclic antidepressants; MAO inhibitors; CNS stimulants; analgesics; antipsychotic agents) should be carefully evaluated. While the contributory role of such medications has not been established, some physicians have discontinued these agents at least 48 hours before and for at least 24 hours following intrathecal use.

Focal and generalized motor seizures have been reported after intrathecal use of water-soluble contrast agents including Iopamidol. In several of these cases reported with Iopamidol, higher than recommended doses were administered. Therefore avoid:

- Deviations from recommended neurodiagnostic procedure or patient management.
- Use in patients with a history of epilepsy unless medically justified.
- Overdosage.
- Intracerebral entry of a bolus or premature diffusion of a high concentration of the medium.
- Failure to maintain elevation of the head during the procedure, on the stretcher, and in bed.
- Excessive and particularly active patient movement or straining.

PRECAUTIONS

General
Diagnostic procedures which involve the use of any radiopaque agent should be carried out under the direction of personnel with the requisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reaction to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions may occur.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease). Patients should be well hydrated prior to and following Iopamidol administration.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (see ADVERSE REACTIONS). Patients at increased risk include those with a history of a previous reaction to a contrast medium, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity (bronchial asthma, hay fever, and food allergies). The occurrence of severe idiosyncratic reactions has prompted the use of several pre-testing methods. However, pre-testing cannot be relied upon to predict adverse reactions as may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pre-testing in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised. Pre-medication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered (see CONTRAINDICATIONS). Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

The possibility of inducing bacterial meningitis in patients during intrathecal procedures should always be considered. To avoid bacterial contamination during spinal puncture, a sterile field should be maintained at all times.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Information for Patients

- Patients receiving injectable radiopaque diagnostic agents should be instructed to:
1. Inform your physician if you are pregnant.
 2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homocystinuria, sickle cell disease, or known thyroid disorder.
 3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of substances used for x-ray procedures (see PRECAUTIONS, General).
 4. Inform your physician about any other medications you are currently taking, including nonprescription drugs, before you have this procedure.

Drug Interactions

Other drugs should not be administered with Iopamidol (see CONTRAINDICATIONS, and DOSAGE AND ADMINISTRATION, Drug Incompatibilities).

Drug/Laboratory Test Interactions

The results of pH and radioactive iodine uptake studies, which depend on iodine estimations, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Any test which might be affected by contrast media should be performed prior to administration of the contrast medium.

Laboratory Test Findings

In vitro studies with animal blood showed that many radiopaque contrast agents, including Iopamidol, produced a slight depression of plasma coagulation factors including prothrombin time, partial thromboplastin time, and fibrinogen, as well as a slight tendency to cause platelet and/or red blood cell aggregation.

Transitory changes may occur in red cell and leukocyte counts, serum calcium, serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), and uric acid in urine. Transient albuminuria may occur.

These findings have not been associated with clinical manifestations. Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term studies in animals have not been performed to evaluate carcinogenic potential. No evidence of genetic toxicity was obtained in *in vitro* tests.

Pregnancy; Teratogenic Effects

Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at doses up to 2.7 and 1.4 times the maximum recommended human dose (1.48 µg/kg in a 50 kg individual), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to Iopamidol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Iopamidol is administered to a nursing woman.

Usual Dosage

See DOSAGE AND ADMINISTRATION section.

ADVERSE REACTIONS

The most frequently reported adverse reactions following intrathecal administration of Iopamidol are headache, nausea, vomiting, and musculoskeletal pain. These reactions usually occur 1 to 10 hours after injection, almost all occurring within 24 hours. They are usually mild to moderate in degree, lasting for a few hours and usually disappearing within 24 hours. Rarely, headaches may be severe or persist for days. Headache is often accompanied by nausea and vomiting

and tends to be more frequent and persistent in patients not optimally hydrated. Backache, neck stiffness, numbness and paresthesias, leg or sciatic-type pain occurred less frequently, often in the form of a transient exacerbation of preexisting symptomsatology. Transient alterations in vital signs may occur and their significance must be assessed on the individual basis.

The following table of incidence of reactions is based on clinical studies with Iopamidol in about 686 patients:

System	Adverse Reactions	
	Estimated Overall Incidence >1%	<1%
Body as a Whole	headache (16.4%)	myopia muscle weakness hot flashes malaise talgia weakness
Digestive	nausea (7.3%) vomiting (6.8%) back pain (2.2%) leg pain (1.4%) neck pain (1.1%)	diarrhea heartburn leg cramps sofaica cervicobrachial irritation meningeal irritation radicular irritation lumbosacral other musculoskeletal pain
Musculoskeletal		involuntary movement burning sensation
Cardiovascular	hypertension (1.1%)	tachycardia hypertension chest pain
Nervous	none	emotional stress dizziness paresthesia confusion hallucinations lightheadedness syncope numbness cold extremities ataxia unsteadiness
Urogenital	none	urinary retention
Respiratory	none	dyspnea
Skin and Appendages	none	rash
Miscellaneous	none	injection site pain

Other adverse effects reported in clinical literature for Iopamidol include facial neuralgia, tinnitus, and sweating.
Major motor seizures have been reported in the clinical literature and since market introduction in the United States. Early onset of seizures (less than two hours) is indicative of early substantial intracranial entry. Transitory EEG changes occur and usually take the form of slow wave activity.

While not observed in controlled clinical studies with Iopamidol, the following adverse reactions may occur because they have been reported with Iopamidol and other nonionic water-soluble contrast agents: cardiovascular (arrhythmias); pulmonary (apnea); bacterial meningitis, and aseptic meningitis syndrome; allergy or idiosyncrasy (chills, pruritus, nasal congestion, Guillain-Barre syndrome), CNS irritation (psycho-organic syndrome, mild and transitory perceptual aberrations such as depersonalization, anxiety, depression, hyperesthesia, disturbances in speech, sight, or hearing, and disorientation), in addition, hyperreflexia or areflexia, hypertension or hypotension, restlessness, tremor, tachycardia, ataxia, ataxia or dysphasia have occurred). Profound mental disturbances have rarely been reported (various forms and degrees of aphasia, mental confusion or disorientation); the onset is usually at 8 to 10 hours and lasts for about 24 hours without aftereffects. However, occasionally they have been manifest as apprehension, agitation, or progressive withdrawal to the point of stupor or coma. In a few cases, these have been accompanied by transitory hearing loss or other auditory symptoms and visual disturbances (believed subjective or delusional). Persistent



IOPAMIDOL-M 200
Iopamidol Injection USP, 41%
IOPAMIDOL-M 300
Iopamidol Injection USP, 61%

DIAGNOSTIC NONIONIC RADIOPAQUE CONTRAST MEDIA
For Intrathecal Administration in Neurodiagnostic Imaging Myelography (Lumbar, Thoracic, Cervical, Total Columnar), Pediatric Myelography (Lumbar, Thoracic), and for Contrast Enhancement of Computed Tomographic (CT), Osteomyelography and Ventriculography

DESCRIPTION
IOPAMIDOL-M (Iopamidol Injection) formulations are stable, aqueous, sterile, and nonpyrogenic solutions for intrathecal administration.

Each mL of IOPAMIDOL-M 200 (Iopamidol Injection USP, 41%) provides 408 mg Iopamidol with 1 mg bromethamine and 0.26 mg edetate calcium disodium. The solution contains approximately 0.022 mg (0.001 mEq) sodium and 200 mg organically bound iodine per mL.

Each mL of IOPAMIDOL-M 300 (Iopamidol Injection USP, 61%) provides 612 mg Iopamidol with 1 mg bromethamine and 0.39 mg edetate calcium disodium. The solution contains approximately 0.043 mg (0.002 mEq) sodium and 300 mg organically bound iodine per mL.

cortical loss of vision in association with convulsions, and ventricular block have been reported. Rarely, persistent through transitory weakness in the leg or ocular muscles has been reported. *Peripheral neuropathies* have been rare and transitory. They include sensory and/or motor or nerve root disturbances, myelitis, persistent leg muscle pain or weakness, or sixth nerve palsy, or cauda equina syndrome. Muscle cramps, fasciculation or myoclonia, spinal convulsion, paralysis, or spasticity are unusual.

General Adverse Reactions To Contrast Media

Reactions known to occur with parenteral administration of iodinated ionic contrast agents (see the listing below) are possible with any ionic agent. Approximately 95 percent of adverse reactions accompanying the use of other water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Reported incidences of death from the administration of other iodinated contrast media range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005 percent) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions. Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels induced by the contrast medium are included in this category. During intrathecal use, there is a lower incidence of electroencephalographic changes as well as neurotoxicity by virtue of the intrinsic properties of the iopamidol molecule.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of drug injected, the speed of injection, the mode of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration. The severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that for the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations. Most adverse reactions to intravascular contrast agents appear within one to three minutes after the start of injection, but delayed reactions may occur (see PRECAUTIONS, General).

Because measurable plasma levels are attained following the intrathecal administration of iopamidol, adverse reactions reported with the use of intravascular contrast agents are theoretically possible. These include:

Cardiovascular: vasodilation (feeling of warmth), cerebral hematomas, hemodynamic disturbances, sinus bradycardia, transient electrocardiographic abnormalities, ventricular fibrillation, petechiae.

Digestive: nausea, vomiting, severe unilateral or bilateral swelling of the parotid and submaxillary glands.

Nervous: paresthesia, dizziness, dyspnea, laryngeal edema, pulmonary edema, bronchospasm, rhinitis.

Respiratory: increased cough, asthma, dyspnea, laryngeal edema, pulmonary edema, bronchospasm, rhinitis.

Skin and Appendages: injection site pain usually due to extravasation and/or erythematous swelling, skin necrosis, urticaria.

Urogenital: osmotic nephrosis of proximal tubular cells, renal failure, pain.

Special Senses: perversion of taste, bilateral ocular irritation; lacrimation; itching; conjunctival chemosis, infection, and conjunctivitis.

The following reactions may also occur: neutropenia, thrombocytopenia, flushing, pallor, weakness, severe retching and choking, wheezing, cramps, and sneezing.

OVERDOSAGE
A dose of 3000 mg in adults and 2400 mg in children is sufficient for most myelographic procedures. Doses above these levels may result in an increased frequency and severity of adverse reactions including seizures. However, in myelography, even use

of a recommended dose can produce mental aberrations tantamount to overdosage, if incorrect management of the patient during or immediately following the procedure permits inadvertent early intracranial entry of a large portion of the medium.

Treatment of an overdose of an injectable radiopaque contrast medium is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

DOSE AND ADMINISTRATION

In adults a solution that is approximately isotonic (IOPAMIDOL-M 200) is recommended for examination of the lumbar region. For examination of the contrast medium to distant target areas, the more concentrated IOPAMIDOL-M 300 preparation should be used to compensate for dilution of IOPAMIDOL-M (Iopamidol Injection) with cerebrospinal fluid.

The usual recommended adult dose range for iopamidol is 2000-3000 mg iodine. Iopamidol formulated to contain more than 300 mg/mL should not be used intrathecally in adults. The minimum dose needed to perform a procedure should always be used.

In pediatric patients, a solution that is approximately isotonic (Iopamidol-M 200) is recommended for all intrathecal procedures. In children, loss of contrast due to mixing on movement of the medium is less apt to occur because of their shorter spinal cord.

The usual recommended pediatric dose range for Iopamidol is 1400-2400 mg iodine. Iopamidol formulated to contain more than 200 mg/mL should not be used intrathecally in children. The minimum dose needed to perform a procedure should always be used. See pediatric dosage table for recommended dosage.

Anesthesia is not necessary. However, young children may require general anesthesia for technical reasons. Premedication with sedatives or tranquilizers is usually not needed. In patients with a history of seizure activity who are not on anticonvulsant therapy, premedication with barbiturates or phenytoin should be considered.

Lumbar puncture is usually made between L3 and L4, if pathologic is suspected at this level, the interspace immediately above or below may be selected. A lateral cervical puncture may also be used.

Rate of Injection: To avoid excessive mixing with cerebrospinal fluid and consequent loss of contrast as well as premature cephalad dispersion, injection must be made slowly over one to two minutes; the needle may then be removed.

An interval of at least 48 hours should be allowed before repeat examination, however, whenever possible five to seven days is recommended.

As with all radiopaque contrast agents, only the lowest dose of IOPAMIDOL-M necessary to obtain adequate visualization should be used. A lower dose reduces the possibility of an adverse reaction. Most procedures do not require use of either a maximum dose or the highest available concentration of IOPAMIDOL-M; the combination of dose and IOPAMIDOL-M concentration to be used should be carefully individualized, and factors such as age, body size, anticipated pathology and degree and extent of opacification required, structural lesions, and equipment and technique to be employed should be considered. Following are the usual recommended pediatric and adult doses of IOPAMIDOL-M.

The pediatric doses listed below, intended as a guideline, are based on age rather than weight because the brain and CSF capacity is independent of weight. Variations will depend on such factors as height, suspected pathology, the patient's condition, technique used, etc. (e.g. CT or standard radiology or movement of the contrast media directed distal to the site of injection).

Pediatric Dosage Table
Iopamidol-M 200 (200 mg/mL)

Procedure	Usual Recommended Dose (mL)	
	Age Years	Dose (mL)
Lumbar, thoracic myelogram	2-7	7-8
	8-12	8-11
	13-18	10-12

Adult Dosage Table

Procedure	Usual Recommended Dose	
	Concentration Of Solution (mg/mL)	Dose (mL)
Lumbar myelogram	200	10 to 15
Thoracic myelogram	200	10 to 15
Cervical myelogram	200	10 to 15

(via lumbar injection)	300	10
Cervical myelogram (via lateral cervical injection)	200	10
Total columnar myelography	300	10
CT myelography (via lumbar injection)	200	4 to 6

Following subarachnoid injection, conventional radiography will continue to provide good diagnostic contrast for at least 30 minutes. At about one hour, diagnostic degree of contrast will not usually be available. However, sufficient contrast for CT myelography myelography should be deferred for at least four hours to reduce the degree of contrast.

Aspiration of iopamidol is unnecessary following intrathecal administration (see CLINICAL PHARMACOLOGY).

It is desirable that solutions of radiopaque agents for intrathecal use be at body temperature when injected. In the event that crystallization of the medium has occurred, place the vial in hot (80°-100°C) water for about five minutes, then shake gently to obtain a clear solution. Cool to body temperature before use. Discard vial without use if solids persist.

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile syringes. Spinal puncture must always be performed under sterile conditions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Iopamidol solutions should be used only if clear and within the normal colorless to pale yellow range. Patients should be well hydrated prior to and following IOPAMIDOL-M (Iopamidol Injection) administration.

Suggestions for Usual Patient Management

- Preprocedure**
- See WARNINGS regarding discontinuation of neuroleptic agents.
 - Maintain normal diet up to 2 hours before procedure.
 - Ensure hydration—fluids up to time of procedure.

- During Procedure**
- Use minimum dose and concentration required for satisfactory contrast.
 - Inject slowly over 1 to 2 minutes to avoid excessive mixing with CSF.
 - Abrupt or active patient movement causes excessive mixing with CSF.

- Instruct patient to remain passive. Move patient slowly and only as necessary.
- To maintain as a bolus, move medium to distal area very slowly under fluoroscopic control.

- In all positioning techniques keep the patient's head elevated above highest level of spine.
- Do not lower head of table more than 15° during thoraco-cervical procedures.

- In patients with excessive lordosis, consider lateral position for injection and movement of the medium cephalad.
- Avoid intracranial entry of a bolus.
- Avoid early and high cephalad dispersion of the medium.

- At completion of direct cervical or lumbo-cervical procedures, raise head of table steeply (45°) for about 2 minutes to restore medium to lower levels.

- Postprocedure**
- Raise head of stretcher to at least 30° before moving patient onto it.
 - Movement onto stretcher, and off the stretcher to bed, should be done slowly with patient completely passive, maintaining head up position.

- Before moving patient onto bed, raise head of bed 30° to 45° and maintain the patient in this position under close observation for 12 to 24 hours.
- Advise patient to remain still in bed in head up position for the first 24 hours.

- Obtain visitors cooperation in keeping the patient quiet and in head up position, especially in first few hours.
- Encourage oral fluids and diet as tolerated.

- Anticholinergics of the phenothiazine class should not be administered to treat postprocedural nausea or vomiting (see WARNINGS). Since persistent nausea and vomiting may result in dehydration, prompt consideration of volume replacement by intravenous fluids is recommended.

Drug Incompatibilities

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

HOW SUPPLIED

IOPAMIDOL-M 200 (Iopamidol Injection USP, 41%)
Ten 15 mL single dose bottles (NDC 58707-007-14)

IOPAMIDOL-M 300 (Iopamidol Injection USP, 61%)
Ten 15 mL single dose bottles (NDC 58707-005-14)

Iopamidol formulations are supplied in single dose containers. Discard unused portion.

Rx only

Storage

Store at controlled room temperature 20-25°C (68-77°F) [see USP]. Protect from light.

Cook Imaging Corporation
Bloomington, Indiana 47403

Distributed by Cook Incorporated, Bloomington, Indiana 47402

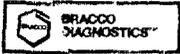
For further information or ordering, call 1-800-467-4500

Printed in U.S.A.
Prepared July, 2000
03-118-853

Approved by:
Kelly Davis
7/20/00

Reference Drug Labeling

Isovue-M, 200 mgI/mL, Vial Label

 **BRACCO DIAGNOSTICS**

20 mL NDC 0270-1411-25
20% Organically Bound Iodine
ISOVUE-M® 200
Iopamidol Injection 41%

Caution: Federal law prohibits dispensing without prescription

For Intravenous Use • Each mL of Iodine
Equivalent to 200 mg of Iodine
400 mg Iopamidol with 1 mg Bromothalamine and
0.38 mg Levodopa sodium dihydrate, pH adjusted
to 6.5-7.5 with hydrochloric acid and/or sodium
hydroxide. Each mL contains approx. 0.029 mg
sodium and 200 mg organically
bound iodine.

**SEE INSERT FOR INDICATIONS
AND USAGE INFORMATION**

Single Dose Vial • Discard Unused Portion
Protect from Light • Store at Controlled Room
Temperature

Bracco Diagnostics Inc.
Princeton, NJ 08543
E.R. Squibb & Sons Inc.
New Brunswick, NJ 08903
Made in USA

027014125
C0573F / D125

Isovue-M, 300 mgI/mL, Vial Label

 **BRACCO DIAGNOSTICS**

15 mL NDC 0270-1412-15
30% Organically Bound Iodine
ISOVUE-M® 300
Iopamidol Injection 61%

Caution: Federal law prohibits dispensing without prescription

For Intravenous Use • SEE INSERT FOR INDICATIONS
AND USAGE INFORMATION. Each mL of Iodine
Equivalent to 300 mg of Iodine
600 mg Iopamidol with 1 mg Bromothalamine and 0.38 mg
Levodopa sodium dihydrate, pH adjusted to 6.5-7.5
with hydrochloric acid and/or sodium hydroxide. Each
mL contains approximately 0.043 mg (0.002 mEq)
sodium and 300 mg organically bound iodine.

Single Dose Vial • Discard unused portion
Protect from Light
Store at controlled room temperature

Bracco Diagnostics Inc., Princeton, NJ 08543
Manufactured for
E.R. Squibb & Sons Inc., New Brunswick, NJ 08903
Made in USA


027014125
C0573F / D125

EXP: JUN 2001
SEP 2006

Isovue-M, 200 mgI/mL, Box Label



1 box • 10 vials
10 mL each

NDC 0270-1411-11

20% Organically Bound Iodine

ISOVUE-M® 200

Iopamidol Injection 41%

Manufactured for
Bracco Diagnostics Inc.
Princeton, NJ 08543
by E.R. Squibb & Sons Inc.
New Brunswick, NJ 08903

EXP. OCT 2002
9K29999

For Intrathecal Use

SEE INSERT FOR INDICATIONS AND DOSAGE INFORMATION
Each mL of sterile, nonpyrogenic, aqueous solution provides 408 mg iopamidol with 1 mg tromethamine and 0.26 mg edetate calcium disodium; pH adjusted to 6.5–7.5 with hydrochloric acid and/or sodium hydroxide. Each mL contains approximately 0.029 mg (0.001 mEq) sodium and 200 mg organically bound iodine.

SINGLE DOSE VIALS • DISCARD UNUSED PORTION
Keep cover closed to protect vials from exposure to light
Store at controlled room temperature.

Caution: Federal law prohibits dispensing without prescription
US Patent 4,001,323
Made in USA



(01)30302701411118(30)1

C5702C / D1111



Isovue-M, 300 mgI/mL, Box Label



1 box • 10 vials
15 mL each

NDC 0270-1412-15

30% Organically Bound Iodine

ISOVUE-M® 300

Iopamidol Injection 61%

Manufactured for
Bracco Diagnostics Inc.
Princeton, NJ 08543
by E.R. Squibb & Sons Inc.
New Brunswick, NJ 08903

EXP. JAN 2003
0A37958

For Intrathecal Use

SEE INSERT FOR INDICATIONS AND DOSAGE INFORMATION
Each mL of sterile, nonpyrogenic, aqueous solution provides 612 mg iopamidol with 1 mg tromethamine and 0.39 mg edetate calcium disodium; pH adjusted to 6.5–7.5 with hydrochloric acid and/or sodium hydroxide. Each mL contains approximately 0.043 mg (0.002 mEq) sodium and 300 mg organically bound iodine.

SINGLE DOSE VIALS • DISCARD UNUSED PORTION
Keep cover closed to protect vials from exposure to light
Store at controlled room temperature.

Caution: Federal law prohibits dispensing without prescription
US Patent 4,001,323
Made in USA

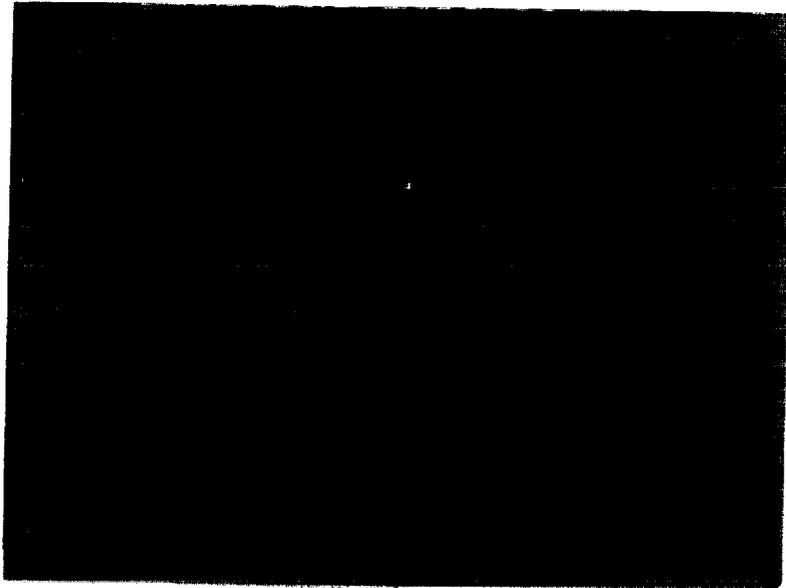


(01)30302701412153(30)1

C8779E / D1215



Isovue-M Nursing Notice



Isovue-M Package Insert



ISOVUE®-200
Iopamidol Injection 41%

ISOVUE®-250
Iopamidol Injection 51%

ISOVUE®-300
Iopamidol Injection 61%

ISOVUE®-370
Iopamidol Injection 76%

NOT FOR INTRATHECAL USE

Isovue 200, 250, 300 and 370 are NOT FOR INTRATHECAL USE.
See Indications, and Dosage and Administration for further details on proper use.

**DIAGNOSTIC
NONIONIC RADIOPAQUE CONTRAST MEDIA**
For Angiography Throughout the Cardiovascular System, including Cerebral and Peripheral Arteriography, Coronary Arteriography and Ventriculography, Pediatric Angiocardiography, Selective Visceral Arteriography and Aortography, Peripheral Venography (Phlebography), and Adult and Pediatric Intravenous Excretory Urography and Intravenous Adult and Pediatric Contrast Enhancement of Computed Tomographic (CECT) Head and Body Imaging

DESCRIPTION

ISOVUE (Iopamidol Injection) formulations are stable, aqueous, sterile, and nonpyrogenic solutions for intravascular administration.

Each mL of ISOVUE-200 (Iopamidol Injection 41%) provides 408 mg Iopamidol with 1 mg tromethamine and 0.26 mg edetate calcium disodium. The solution contains approximately 0.029 mg (0.001 mEq) sodium and 200 mg organically bound iodine per mL.

Each mL of ISOVUE-250 (Iopamidol Injection 51%) provides 510 mg Iopamidol with 1 mg tromethamine and 0.33 mg edetate calcium disodium. The solution contains approximately 0.036 mg (0.002 mEq) sodium and 250 mg organically bound iodine per mL.

Each mL of ISOVUE-300 (Iopamidol Injection 61%) provides 612 mg Iopamidol with 1 mg tromethamine and 0.39 mg edetate calcium disodium. The solution contains approximately 0.043 mg (0.002 mEq) sodium and 300 mg organically bound iodine per mL.

Each mL of ISOVUE-370 (Iopamidol Injection 76%) provides 755 mg Iopamidol with 1 mg tromethamine and 0.48 mg edetate calcium disodium. The solution contains approximately 0.053 mg (0.002 mEq) sodium and 370 mg organically bound iodine per mL.

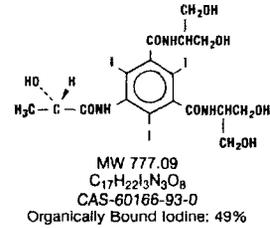
The pH of ISOVUE contrast media has been adjusted to 6.5-7.5 with hydrochloric acid and/or sodium hydroxide. Pertinent physicochemical data are noted below. ISOVUE (Iopamidol Injection) is hypertonic as compared to plasma and cerebrospinal fluid (approximately 285 and 301 mOsm/kg water, respectively).

Parameter	41%	51%	61%	Iopamidol 76%
Concentration (mg/mL)	200	250	300	370
Osmolality @ 37° C (mOsm/kg water)	413	524	616	796
Viscosity (cP) @ 37° C	2.0	3.0	4.7	9.4
@ 20° C	3.3	5.1	8.8	20.9
Specific Gravity @ 37° C	1.227	1.281	1.339	1.405

J3-720D



Iopamidol is designated chemically as (S)-N,N'-bis[2-hydroxy-1-(hydroxymethyl)-ethyl]-2,4,6-triiodo-5-lactamidoisophthalamide. Structural formula:



CLINICAL PHARMACOLOGY

Intravascular injection of a radiopaque diagnostic agent opacifies those vessels in the path of flow of the contrast medium, permitting radiographic visualization of the internal structures of the human body until significant hemodilution occurs.

Following intravascular injection, radiopaque diagnostic agents are immediately diluted in the circulating plasma. Calculations of apparent volume of distribution at steady-state indicate that Iopamidol is distributed between the circulating blood volume and other extracellular fluid; there appears to be no significant deposition of Iopamidol in tissues. Uniform distribution of Iopamidol in extracellular fluid is reflected by its demonstrated utility in contrast enhancement of computed tomographic imaging of the head and body following intravenous administration.

The pharmacokinetics of intravenously administered Iopamidol in normal subjects conform to an open two-compartment model with first order elimination (a rapid alpha phase for drug distribution and a slow beta phase for drug elimination). The elimination serum or plasma half-life is approximately two hours; the half-life is not dose dependent. No significant metabolism, deiodination, or biotransformation occurs.

Iopamidol is excreted mainly through the kidneys following intravascular administration. In patients with impaired renal function, the elimination half-life is prolonged dependent upon the degree of impairment. In the absence of renal dysfunction, the cumulative urinary excretion for Iopamidol, expressed as a percentage of administered intravenous dose, is approximately 35 to 40 percent at 60 minutes, 80 to 90 percent at 8 hours, and 90 percent or more in the 72- to 96-hour period after administration. In normal subjects, approximately one percent or less of the administered dose appears in cumulative 72- to 96-hour fecal specimens.

ISOVUE may be visualized in the renal parenchyma within 30-60 seconds following rapid intravenous administration. Opacification of the calyces and pelvis in patients with normal renal function becomes apparent within 1 to 3 minutes, with optimum contrast occurring between 5 and 15 minutes. In patients with renal impairment, contrast visualization may be delayed.

Iopamidol displays little tendency to bind to serum or plasma proteins. No evidence of *in vivo* complement activation has been found in normal subjects.

Animal studies indicate that Iopamidol does not cross the blood-brain barrier to any significant extent following intravascular administration.

ISOVUE (Iopamidol Injection) enhances computed tomographic brain imaging through augmentation of radiographic efficiency. The degree of enhancement of visualization of tissue density is directly related to the iodine content in an administered dose; peak iodine blood levels occur immediately following rapid injection of the dose. These levels fall rapidly within five to ten minutes. This can be accounted for by the dilution in the vascular and extracellular fluid compartments which causes an initial sharp fall in plasma concentration. Equilibration with the extracellular compartments is reached in about ten minutes; thereafter, the fall becomes exponential. Maximum contrast enhancement frequently occurs after peak blood iodine levels are reached. The delay in maximum contrast enhancement can range from five to forty minutes depending on the peak iodine levels achieved and the cell type of the lesion. This lag suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine within the lesion and outside the blood pool, although the mechanism by which this occurs is not clear. The radiographic enhancement of nontumoral lesions, such as arteriovenous malformations and aneurysms, is probably dependent on the iodine content of the circulating blood pool.

In CECT head imaging, ISOVUE (Iopamidol Injection) does not accumulate in normal brain tissue due to the presence of the blood-brain barrier. The increase in x-ray absorption in normal brain is due to the presence of contrast agent within the blood pool. A break in the blood-brain barrier such as occurs in malignant tumors of the brain allows the accumulation of the contrast medium within the interstitial tissue of the tumor. Adjacent normal brain tissue does not contain the contrast medium.

In nonneural tissues (during computed tomography of the body), Iopamidol diffuses rapidly from the vascular into the extravascular space. Increase in x-ray absorption is related to blood flow, concentration of the contrast medium, and extraction of the contrast medium by interstitial tissue of tumors since no barrier exists. Contrast enhancement is thus due to the relative differences in extravascular diffusion between normal and abnormal tissue, quite different from that in the brain.

The pharmacokinetics of iopamidol in both normal and abnormal tissue have been shown to be variable. Contrast enhancement appears to be greatest soon after administration of the contrast medium, and following intraarterial rather than intravenous administration. Thus, greatest enhancement can be detected by a series of consecutive two- to three-second scans performed just after injection (within 30 to 90 seconds), i.e., dynamic computed tomographic imaging.

INDICATIONS AND USAGE

ISOVUE (Iopamidol Injection) is indicated for angiography throughout the cardiovascular system, including cerebral and peripheral arteriography, coronary arteriography and ventriculography, pediatric angiocardiology, selective visceral arteriography and aortography, peripheral angiography (phlebography), and adult and pediatric intravenous excretory urography and intravenous adult and pediatric contrast enhancement of computed tomographic (CECT) head and body imaging (see below).

CECT Head Imaging

ISOVUE may be used to refine diagnostic precision in areas of the brain which may not otherwise have been satisfactorily visualized.

Tumors

ISOVUE may be useful to investigate the presence and extent of certain malignancies such as: gliomas including malignant gliomas, glioblastomas, astrocytomas, oligodendrogliomas and gangliomas, ependymomas, medulloblastomas, meningiomas, neuromas, pinealomas, pituitary adenomas, cranio-pharyngiomas, germinomas, and metastatic lesions. The usefulness of contrast enhancement for the investigation of the retrolubular space and in cases of low grade or infiltrative glioma has not been demonstrated.

In calcified lesions, there is less likelihood of enhancement. Following therapy, tumors may show decreased or no enhancement.

The opacification of the inferior vermis following contrast media administration has resulted in false-positive diagnosis in a number of otherwise normal studies.

Nonneoplastic Conditions

ISOVUE may be beneficial in the image enhancement of nonneoplastic lesions. Cerebral infarctions of recent onset may be better visualized with contrast enhancement, while some infarctions are obscured if contrast media are used. The use of iodinated contrast media results in contrast enhancement in about 60 percent of cerebral infarctions studied from one to four weeks from the onset of symptoms.

Sites of active infection may also be enhanced following contrast media administration.

Arteriovenous malformations and aneurysms will show contrast enhancement. For these vascular lesions, the enhancement is probably dependent on the iodine content of the circulating blood pool.

Hematomas and intraparenchymal bleeders seldom demonstrate any contrast enhancement. However, in cases of intraparenchymal clot, for which there is no obvious clinical explanation, contrast media administration may be helpful in ruling out the possibility of associated arteriovenous malformation.

CECT Body Imaging

ISOVUE (Iopamidol Injection) may be used for enhancement of computed tomographic images for detection and evaluation of lesions in the liver, pancreas, kidneys, aorta, mediastinum, abdominal cavity, pelvis and retroperitoneal space.

Enhancement of computed tomography with ISOVUE may be of benefit in establishing diagnoses of certain lesions in these sites with greater assurance than is possible with CT alone, and in supplying additional features of the lesions (e.g., hepatic abscess delineation prior to percutaneous drainage). In other cases, the contrast agent may allow visualization of lesions not seen with CT alone (e.g., tumor extension), or may help to define suspicious lesions seen with unenhanced CT (e.g., pancreatic cyst).

Contrast enhancement appears to be greatest within 60 to 90 seconds after bolus administration of contrast agent. Therefore, utilization of a continuous scanning technique ("dynamic CT scanning") may improve enhancement and diagnostic assessment of tumor and other lesions such as an abscess, occasionally revealing unsuspected or more extensive disease. For example, a cyst may be distinguished from a vascularized solid lesion when precontrast and enhanced scans are compared; the nonperfused mass shows unchanged x-ray absorption (CT number). A vascularized lesion is characterized by an increase in CT number in the few minutes after a bolus of intravascular contrast agent; it may be malignant, benign, or normal tissue, but would probably not be a cyst, hematoma, or other nonvascular lesion.

Because unenhanced scanning may provide adequate diagnostic information in the individual patient, the decision to employ contrast enhancement, which may be associated with risk and increased radiation exposure, should be based upon a careful evaluation of clinical, other radiological, and unenhanced CT findings.

CONTRAINDICATIONS

None.

WARNINGS

Severe Adverse Events—Inadvertent Intrathecal Administration

Serious adverse reactions have been reported due to the inadvertent intrathecal administration of iodinated contrast media that are not indicated for intrathecal use. These serious adverse reactions include: death, convulsions, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, seizures, rhabdomyolysis, hyperthermia, and brain edema. Special attention must be given to insure that this drug product is not inadvertently administered intrathecally.

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 nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic 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 with heparinized saline solutions, and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

Caution must be exercised in patients with severely impaired renal function, those with combined renal and hepatic disease, or anuria, particularly when larger doses are administered.

Radiopaque diagnostic contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication; however, special precautions are required.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when injected intravenously or intraarterially.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure and measures for treatment of a hypertensive crisis should be available. These patients should be monitored very closely during contrast enhanced procedures.

Reports of thyroid storm following the use of iodinated radiopaque diagnostic agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS

General

Diagnostic procedures which involve the use of any radiopaque agent should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reaction to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions may occur.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease). Patients should be well hydrated prior to and following iopamidol administration.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (see ADVERSE REACTIONS). Patients at increased risk include those with a history of a previous reaction to a contrast medium, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity (bronchial asthma, hay fever, and food allergies). The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Recent reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported with radiopaque media in anesthetized patients, which may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Even though the osmolality of iopamidol is low compared to diatrizoate or iohalamate based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

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

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiology in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure. Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism. See also Pediatric Use.

In addition to the general precautions previously described, special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic

disease, local infection of a totally obstructed venous system.

Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial or venous disease.

Information for Patients

Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant.
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see **WARNINGS**).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of substances used for x-ray procedures (see **PRECAUTIONS-General**).
4. Inform your physician about any other medications you are currently taking, including non-prescription drugs, before you have this procedure.

Drug Interactions

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of intravascular agents should therefore be postponed in any patient with a known or suspected hepatic or biliary disorder who has recently received a cholecystographic contrast agent.

Other drugs should not be admixed with iopamidol.

Drug/Laboratory Test Interactions

The results of PBI and radioactive iodine uptake studies, which depend on iodine estimations, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Any test which might be affected by contrast media should be performed prior to administration of the contrast medium.

Laboratory Test Findings

In vitro studies with animal blood showed that many radiopaque contrast agents, including iopamidol, produced a slight depression of plasma coagulation factors including prothrombin time, partial thromboplastin time, and fibrinogen, as well as a slight tendency to cause platelet and/or red blood cell aggregation (see **PRECAUTIONS-General**).

Transitory changes may occur in red cell and leucocyte counts, serum calcium, serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), and uric acid in urine; transient albuminuria may occur.

These findings have not been associated with clinical manifestations.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. No evidence of genetic toxicity was obtained in *in vitro* tests.

Pregnancy: Teratogenic Effects

Pregnancy Category B Reproduction studies have been performed in rats and rabbits at doses up to 2.7 and 1.4 times the maximum recommended human dose (1.48 g/kg in a 50 kg individual), respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to iopamidol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when iopamidol is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children has been established in pediatric angiocardiology, computed tomography (head and body) and excretory urography. Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, cyanotic heart disease, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS

Adverse reactions following the use of iopamidol are usually mild to moderate, self-limited, and transient.

In angiocardiology (597 patients), the adverse reactions with an estimated incidence of one percent or higher are: hot flashes 3.4%; angina pectoris 3.0%; flushing 1.8%; bradycardia 1.3%; hypotension 1.0%; hives 1.0%.

In a clinical trial with 76 pediatric patients undergoing angiocardiology, 2 adverse reactions (2.6%) both remotely attributed to the contrast media were reported. Both patients were less than 2 years of age, both had cyanotic heart disease with underlying right ventricular abnormalities and abnormal pulmonary circulation. In one patient preexisting cyanosis was transiently intensified following contrast media administration. In the second patient preexisting decreased peripheral perfusion was intensified for 24 hours following the examination. (See **"PRECAUTIONS"** Section for information on high risk nature of these patients.)

Intravascular injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral arteriography and venography; pain and warmth are less frequent and less severe with ISOVUE (iopamidol Injection) than with diatrizoate meglumine and diatrizoate sodium injection.

The following table of incidence of reactions is based on clinical studies with ISOVUE in about 2246 patients.

Adverse Reactions

System	Estimated Overall Incidence	
	>1%	≤1%
Cardiovascular	none	tachycardia hypotension hypertension myocardial ischemia circulatory collapse S-T segment depression bigeminy extrasystoles ventricular fibrillation angina pectoris bradycardia transient ischemic attack thrombophlebitis vasovagal reaction tingling in arms grimace faintness vomiting anorexia throat constriction dyspnea pulmonary edema
Nervous	pain (2.8%) burning sensation (1.4%)	rash urticaria pruritus flushing headache fever chills excessive sweating back spasm taste alterations nasal congestion visual disturbances urinary retention
Digestive	nausea (1.2%)	
Respiratory	none	
Skin and Appendages	none	
Body as a Whole	hot flashes (1.5%)	
Special Senses	warmth (1.1%)	
Urogenital	none	

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, or myocardial ischemia or infarction have been reported with Isovue and may occur during coronary arteriography and left ventriculography. Following coronary and ventricular injections, certain electrocardiographic changes (increased QTC, increased R-R, T-wave amplitude) and certain hemodynamic changes (decreased systolic pressure) occurred less frequently with ISOVUE (iopamidol Injection) than with diatrizoate meglumine and diatrizoate sodium injection; increased LVEDP occurred less frequently after ventricular iopamidol injections.

In aortography, the risks of procedures also include injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, accidental selective filling of the right renal artery during the translumbar procedure in the presence of preexisting renal disease, retroperitoneal hemorrhage from the translumbar approach, and spinal cord injury and pathology associated with the syndrome of transverse myelitis.

The following adverse reactions have been reported for iopamidol: **Cardiovascular:** arrhythmia, arterial spasms, flushing, vasodilation, chest pain, cardiopulmonary arrest; **Nervous:** confusion, paresthesia, dizziness, convulsions, paralysis, coma; **Respiratory:** increased cough, sneezing, asthma, apnea, laryngeal edema, chest tightness, rhinitis; **Skin and Appendages:** injection site pain usually due to extravasation and/or erythematous swelling, pallor, periorbital edema, facial edema; **Urogenital:** pain, hematuria; **Special Senses:** watery itchy eyes, lacrimation, conjunctivitis; **Musculoskeletal:** muscle spasm, involuntary leg movement; **Body as a whole:** tremors, malaise, anaphylactoid reaction (characterized by cardiovascular, respiratory, and cutaneous symptoms), pain; **Digestive:** severe retching and choking, abdominal cramps. Some of these may occur as a consequence of the procedure. Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

General Adverse Reactions To Contrast Media

Reactions known to occur with parenteral administration of iodinated ionic contrast agents (see the listing below) are possible with any nonionic agent. Approximately 95 percent of adverse reactions accompanying the use of other water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Reported incidences of death from the administration of other iodinated contrast media range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005 percent) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions. Chemotoxic reactions result from the physico-chemical properties of the contrast medium, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category. Experience with iopamidol suggests there is much less discomfort (e.g., pain and/or warmth) with peripheral arteriography. Fewer changes are noted in ventricular function after ventriculography and coronary arteriography.



Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of drug injected, the speed of injection, the mode of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that for the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations. Most adverse reactions to intravascular contrast agents appear within one to three minutes after the start of injection, but delayed reactions may occur (see **PRECAUTIONS—General**).

In addition to the adverse drug reactions reported for Iopamidol, the following additional adverse reactions have been reported with the use of other intravascular contrast agents and are possible with the use of any water-soluble iodinated contrast agent:

Cardiovascular: cerebral hematomas, petechiae; **Hematologic:** neutropenia; **Skin and Appendages:** skin necrosis; **Urogenital:** osmotic nephrosis of proximal tubular cells, renal failure; **Special Senses:** conjunctival chemosis with infection.

OVERDOSAGE

Treatment of an overdose of an injectable radiopaque contrast medium is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

DOSAGE AND ADMINISTRATION

General

It is desirable that solutions of radiopaque diagnostic agents for intravascular use be at body temperature when injected. In the event that crystallization of the medium has occurred, place the vial in hot (60°-100° C) water for about five minutes, then shake gently to obtain a clear solution. Cool to body temperature before use. Discard vial without use if solids persist.

Withdrawal of contrast agents from their containers should be accomplished under aseptic conditions with sterile syringes. Sterile techniques must be used with any intravascular injection, and with catheters and guidewires.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Iopamidol solutions should be used only if clear and within the normal colorless to pale yellow range.

Patients should be well hydrated prior to and following ISOVUE (Iopamidol Injection) administration.

As with all radiopaque contrast agents, only the lowest dose of ISOVUE necessary to obtain adequate visualization should be used. A lower dose reduces the possibility of an adverse reaction. Most procedures do not require use of either a maximum dose or the highest available concentration of ISOVUE; the combination of dose and ISOVUE concentration to be used should be carefully individualized, and factors such as age, body size, size of the vessel and its blood flow rate, anticipated pathology and degree and extent of opacification required, structure(s) or area to be examined, disease processes affecting the patient, and equipment and technique to be employed should be considered.

Cerebral Arteriography

ISOVUE-300 (Iopamidol Injection, 300 mg/mL) should be used. The usual individual injection by carotid puncture or transfemoral catheterization is 8 to 12 mL, with total multiple doses ranging to 90 mL.

Peripheral Arteriography

ISOVUE-300 usually provides adequate visualization. For injection into the femoral artery or subclavian artery, 5 to 40 mL may be used; for injection into the aorta for a distal runoff, 25 to 50 mL may be used. Doses up to a total of 250 mL of ISOVUE-300 have been administered during peripheral arteriography.

Peripheral Venography (Phlebography)

ISOVUE-200 (Iopamidol Injection, 200 mg/mL) should be used. The usual dose is 25 to 150 mL per lower extremity. The combined total dose for multiple injections has not exceeded 350 mL.

Selective Visceral Arteriography and Aortography

ISOVUE-370 (Iopamidol Injection, 370 mg/mL) should be used. Doses up to 50 mL may be required for injection into the larger vessels such as the aorta or celiac artery; doses up to 10 mL may be required for injection into the renal arteries. Often, lower doses will be sufficient. The combined total dose for multiple injections has not exceeded 225 mL.

Pediatric Angiocardiography

ISOVUE-370 should be used. Pediatric angiocardiography may be performed by injection into a large peripheral vein or by direct catheterization of the heart.

The usual dose range for single injections is provided in the following table:

Age	Single Injection	
	Usual Dose Range	mL
< 2 years		10-15
2-9 years		15-30
10-18 years		20-50

The usual dose for cumulative injections is provided in the following table:

Age	Cumulative Injections	
	Usual Dose Range	mL
< 2 years		40
2-4 years		50
5-9 years		100
10-18 years		125

Coronary Arteriography and Ventriculography

ISOVUE-370 should be used. The usual dose for selective coronary artery injections is 2 to 10 mL. The usual dose for ventriculography, or for nonselective opacification of multiple coronary arteries following injection at the aortic root, is 25 to 50 mL. The total dose for combined procedures has not exceeded 200 mL. EKG monitoring is essential.

Excretory Urography

ISOVUE-250, ISOVUE-300 or ISOVUE-370 may be used. The usual adult dose for ISOVUE-250 is 50 to 100 mL, for ISOVUE-300 is 50 mL and for ISOVUE-370 is 40 mL administered by rapid intravenous injection.

Pediatric Excretory Urography

ISOVUE-250 or ISOVUE-300 may be used. The dosage recommended for use in children for excretory urography is 1.2 mL/kg to 3.6 mL/kg for ISOVUE-250 and 1.0 mL/kg to 3.0 mL/kg for ISOVUE-300. It should not be necessary to exceed a total dose of 30 grams of iodine.

Computed Tomography

ISOVUE-250 or ISOVUE-300 may be used.

CECT OF THE HEAD: The suggested dose for ISOVUE-250 is 130 to 240 mL and for ISOVUE-300 is 100 to 200 mL by intravenous administration. Imaging may be performed immediately after completion of administration.

CECT OF THE BODY: The usual adult dose range for ISOVUE-250 is 130 to 240 mL and for ISOVUE-300 is 100 to 200 mL administered by rapid intravenous infusion, or bolus injection. Equivalent doses of ISOVUE-370, based on organically bound iodine content, may also be used. The total dose for either CECT procedure should not exceed 60 grams of iodine.

Pediatric Computed Tomography

ISOVUE-250 or ISOVUE-300 may be used. The dosage recommended for use in children for contrast enhanced computed tomography is 1.2 mL/kg to 3.6 mL/kg for ISOVUE-250 and 1.0 mL/kg to 3.0 mL/kg for ISOVUE-300. It should not be necessary to exceed a total dose of 30 grams of iodine.

Drug Incompatibilities

Many radiopaque contrast agents are incompatible *in vitro* with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

HOW SUPPLIED

ISOVUE-200 (Iopamidol Injection 41%)
 Ten 50 mL single dose vials (NDC 0270-1314-30)
 Ten 100 mL single dose bottles (NDC 0270-1314-34)
 Ten 200 mL single dose bottles with administration sets (NDC 0270-1314-40)

ISOVUE-250 (Iopamidol Injection 51%)
 Ten 50 mL single dose vials (NDC 0270-1317-05)
 Ten 100 mL single dose bottles (NDC 0270-1317-02)

Ten 150 mL single dose bottles with administration sets (NDC 0270-1317-03)
 Ten 200 mL single dose bottles with administration sets (NDC 0270-1317-01)
 Ten 150 mL power injector syringes (NDC 0270-1317-43)

ISOVUE-300 (Iopamidol Injection 61%)
 Ten 30 mL single dose vials (NDC 0270-1315-25)
 Ten 50 mL single dose vials (NDC 0270-1315-30)

Ten 75 mL single dose bottles (NDC 0270-1315-47)
 Ten 100 mL single dose bottles (NDC 0270-1315-35)
 Ten 150 mL single dose bottles with administration sets (NDC 0270-1315-37)

Ten 150 mL single dose bottles (NDC 0270-1315-50)
 Ten 100 mL power injector syringes (NDC 0270-1315-57)
 Ten 150 mL power injector syringes (NDC 0270-1315-58)

ISOVUE-370 (Iopamidol Injection 76%)
 Ten 20 mL single dose vials (NDC 0270-1316-07)
 Ten 30 mL single dose vials (NDC 0270-1316-47)

Ten 50 mL single dose vials (NDC 0270-1316-30)
 Ten 50 mL single dose bottles (NDC 0270-1316-01)
 Ten 75 mL single dose bottles (NDC 0270-1316-52)

Ten 100 mL single dose bottles (NDC 0270-1316-35)
 Ten 125 mL single dose bottles (NDC 0270-1316-04)
 Ten 150 mL single dose bottles (NDC 0270-1316-37)

Ten 175 mL single dose bottles (NDC 0270-1316-44)
 Ten 200 mL single dose bottles (NDC 0270-1316-40)
 Ten 75 mL power injector syringes (NDC 0270-1316-56)

Ten 100 mL power injector syringes (NDC 0270-1316-57)
 Power injector syringes are supplied with connector tubing.

Storage
 Store at controlled room temperature. Protect from light.

Also Available
 Iopamidol Injection is also available as ISOVUE-M® for intrathecal administration.

Rx only

Manufactured by
 Bracco Diagnostics Inc.
 Princeton, NJ 08543
 by E.R. Squibb & Sons Inc.
 New Brunswick, NJ 08903

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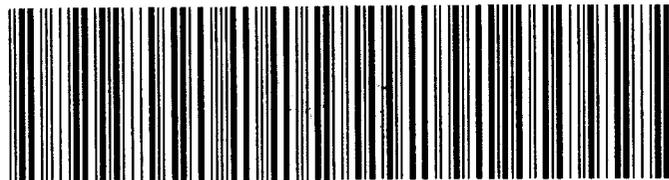
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