PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

CONRAY® 30
(Iothalamate meglumine injection USP 30% w/v)

CONRAY® 43
(Iothalamate meglumine injection USP 43% w/v)

CONRAY® 60
(Iothalamate meglumine injection USP 60% w/v)

Ionic Iodinated Radiographic Contrast Medium for Intravascular Use

Liebel-Flarsheim Canada Inc.
7500 Trans-Canada Highway
Pointe-Claire, QC, H9R 5H8
CANADA

Date of Revision:
December 27, 2017

Submission Control No: 205718

Table of Contents

CONRAY®
Iothalamate Meglumine Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength (w/v)	Clinically Relevant Non-medicinal Ingredients
Intravascular injection	Solution for injection/ 30% , 43% and 60%	Edetate Calcium Disodium USP, Meglumine USP, Monobasic and Sodium phosphate USP. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USES

Conray 60 is indicated for use in excretory urography, cerebral angiography, peripheral arteriography, venography, arthrography, direct cholangiography, endoscopic retrograde cholangiopancreatography, intravenous contrast enhancement in computed tomography and digital subtraction angiography.

Conray 43 is indicated for use in lower extremity venography, intravenous infusion urography and for the intravenous contrast enhancement in computerized tomography of the brain.

Conray 30 is indicated for use in intravenous infusion urography and for contrast enhancement in computerized tomography of the brain.

Geriatrics (> *65* years of age):
No data available.

Pediatrics (*0* - *18* years of age):
See dosage and administration section.

CONTRAINDICATIONS

Conray is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

Conray is contraindicated in patients with anuria or severe oliguria. Arthrography should not be performed if infection is present in or near the joint.

Percutaneous transhepatic cholangiography is contraindicated in patients with coagulation defects and prolonged prothrombin times, until normal or near normal coagulation is achieved. Endoscopic retrograde cholangiography is contraindicated during an acute attack of pancreatitis or during clinically evident cholangitis. The procedure is also contraindicated in patients in whom endoscopic examination is prohibited.

Conray must not be used for myelography or for injection into cysts and sinuses that might communicate with the subarachnoid space.

Conray should not be used for the enhancement of CT brain images in patients suspected of having cranial subarachnoid hemorrhage.

WARNINGS AND PRECAUTIONS

WARNINGS

Ionic iodinated contrast media inhibit blood coagulation more than nonionic contrast media. Nonetheless, it is necessary to avoid prolonged contact of blood with syringes containing all 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, number of injections, 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 keeping guidewires, catheters and all angiographic equipment free of blood, use of manifold systems and/or three way stopcocks, frequent catheter flushing and 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.

Serious or fatal reactions have been associated with the administration of iodine containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

A definite risk exists with the use of intravascular contrast agents in patients who are known to have multiple myeloma. In some instances anuria has developed resulting in progressive uremia, renal failure and eventually death. Although neither the contrast agent nor dehydration has separately proved to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not an absolute contraindication to the procedure; however, partial dehydration in the preparation of these patients for the examination is not recommended since this may predispose to precipitation of myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over 40, should be considered before instituting intravascular administration of contrast agents.

Administration of radiopaque materials to patients known or suspected to have 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.

Contrast media have been shown to promote the phenomenon of sickling in individuals who are homozygous for sickle cell disease when the material is injected intravenously or intra-arterially.

Conray must not be used for myelography or for injection into cysts and sinuses that might communicate with the subarachnoid space.

In computed tomography of the brain, it has been reported that in low density lesions, false negative results may be produced following contrast media administration, e.g. contrast media may obscure low density lesions. Steps should be taken to insure that patients undergoing computed tomography have received no injections of water-soluble contrast media at least 24 hours prior to examination. It is recommended that a computed tomographic brain scan always be obtained prior to the administration of Conray.

Thyroid dysfunction

Conray, like all other iodinated contrast media, may induce changes in thyroid function in some patients. Transient hyperthyroidism or hypothyroidism has been reported following iodinated contrast media administration to adult and pediatric patients.

Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or even more than a month (see ADVERSE REACTIONS). Some patients were treated for hypothyroidism (see PRECAUTIONS – Special populations – Pediatrics - Infants).

PRECAUTIONS

General

All procedures utilizing contrast media carry a definite risk of producing adverse reactions. While most reactions may be minor, life-threatening and fatal reactions may occur without warning. The risk-benefit factor should always be carefully evaluated before such a procedure is undertaken. At all times a fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and training adverse reactions of all severity or situations which may arise as a result of the procedure, should be immediately available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed.

The possibility of an idiosyncratic reaction in patients who have previously received a contrast medium without ill effect should always be considered. Prior to the injection of any contrast medium, the patient should be questioned to obtain a medical history with emphasis on allergy and hypersensitivity. A positive history of bronchial asthma or allergy, a family history of allergy, or a previous reaction or hypersensitivity to a contrast agent may imply a greater than usual risk. Such a history, by suggesting histamine sensitivity and consequently proneness to reactions, may be more accurate than pre-testing in predicting the potential for reaction, although not necessarily the severity or type of reaction in the individual case. A positive history of this type does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but does call for caution. Premedication with antihistamines or corticosteroids to avoid or minimize the possible allergic reactions in such patients should be considered. Under no circumstance should the antihistamine or the corticosteroid be mixed in the same syringe with the contrast medium because of chemical incompatibility.

In order to screen patients for allergy potential, various pretesting procedures have been developed; however, specific literature reports indicate that none of these provocative test procedures can be relied upon to predict severe or fatal reactions. The pre-test most often

performed is the slow intravenous injection of 0.5 to 1.0 mL of the radiopaque medium prior to the injection of the full dose. The absence of a reaction to the test dose does not preclude the possibility of a reaction to the full dose. In some instances, reactions to the test dose itself may be extremely severe; therefore, close observation of the patient and facilities for emergency treatment are indicated.

Caution should be exercised in performing contrast medium studies in patients with endotoxemia and/or those with elevated body temperatures.

Endocrine and Metabolism

Reports of thyroid storm occurring following the intravascular use of iodinated radiopaque 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 this drug.

Conray, like all other contrast media, may induce changes in thyroid function in some patients. Elevation of thyroxine (T4) and/or thyroid-stimulating hormone (TSH) may be observed. Transient thyroid suppression or hypothyroidism has been reported following iodinated contrast media administration to adult and pediatric patients. Decreased level of T4 and triiodothyronine (T3) following the administration in infants were reported to maintain for up to a few weeks or even more than a month (see **ADVERSE REACTIONS**). Hypothyroidism during neonatal period may be harmful for growth and development, including mental development.

Iodine-containing contrast agents may alter the results of thyroid function tests which depend on iodine estimation, e.g. PBI and radioactive iodine uptake studies. Such tests, if indicated, should be performed prior to the administration of this preparation.

Hepatic/Biliary/Pancreatic

See Renal.

Renal

Partial dehydration prior to the examination should be avoided in patients with chronic renal disease, multiple myeloma, diabetes and in infants and small children.

In patients with advanced renal disease, iodinated contrast media should be used with caution, and only when the need for the examination dictates, since excretion of the medium may be impaired. Patients with combined renal and hepatic disease and those with severe hypertension or congestive heart failure may present an additional risk. Renal failure has been reported in patients with liver dysfunction who were given an oral cholecystographic agent, followed by an intravascular iodinated radiopaque agent and also in patients with occult renal disease, notably diabetics and hypertensives.

Administration of Conray should, therefore, be postponed in any patient with a known or suspected hepatic or biliary disorder who has recently taken cholecystographic contrast agent.

Special Populations

Pregnant Women: Reproduction studies with various concentrations of iothalamate sodium, iothalamate meglumine or a combination of both have been performed in mice, rats and rabbits and have revealed no evidence of impaired fertility or harm to the fetus.

There are no well controlled studies in pregnant women but marketing experience does not include any positive evidence of adverse effects on the fetus. Although there is no clearly defined risk such experience cannot exclude the possibility of infrequent or subtle damage to the fetus. Conray should be used in pregnant women only when clearly needed.

Nursing Women: It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken or continued following administration of this drug since many drugs are excreted in human milk.

Pediatrics

Infants : Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of TSH were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or more than a month (see ADVERSE REACTIONS). Hypothyroidism in infants may be harmful for growth and development, including mental development and may require treatment. Thyroid function in infants exposed to ICM should therefore be evaluated and monitored until thyroid function is normalized.

ADVERSE REACTIONS

General

Adverse reactions accompanying the use of iodine-containing intravascular contrast agents are usually mild and transient, although severe and life-threatening reactions, including fatalities, have occurred. Because of the possibility of severe reactions to both the procedure and radiopaque medium, appropriate emergency facilities and well trained personnel should be available to treat both types. These emergency facilities and personnel should remain available for 30-60 minutes following the procedure since severe delayed reactions have been reported.

The following adverse reactions have been observed in conjunction with the use of iodine-

containing intravascular contrast agents.

The most frequent reactions are nausea, vomiting, facial flush and a feeling of body warmth. These are usually of brief duration. Other reactions include the following:

Allergic-type reactions: Dermal manifestations of urticaria with or without pruritus, erythema and maculopapular rash, dry mouth, sweating, conjunctival symptoms, facial, peripheral and angioneurotic edema. Symptoms relating to the respiratory system include sneezing, nasal stuffiness, coughing, choking, dyspnea, chest tightness and wheezing, which may be initial manifestations of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm with or without edema, pulmonary edema, apnea and cyanosis. Rarely, these allergic type reactions can progress into anaphylactic shock with loss of consciousness and coma and severe cardiovascular disturbances.

Cardiovascular reactions: Generalized vasodilatation, flushing and venospasm. Occasionally, thrombosis or, rarely, thrombophlebitis. Red blood cell clumping and agglutination, crenation and interference in clot formation. Extremely rare cases of disseminated intravascular coagulation resulting in death have been reported. Severe cardiovascular responses include rare cases of hypotensive shock, coronary insufficiency, cardiac arrhythmia, fibrillation and arrest. These severe reactions are usually reversible with prompt and appropriate management; however, fatalities have occurred.

Technique reactions: Extravasation with burning pain, hematomas, ecchymosis and tissue necrosis, paresthesia or numbness, vascular constriction due to injection rate, thrombosis and thrombophlebitis, perforation and dissection of blood vessels, dislodgement of atheromatous plaques, injury to neighbouring organs.

Neurological reactions: Spasm, convulsions, aphasia, syncope, paresis, paralysis resulting from spinal cord injury and pathology associated with the syndrome of transverse myelitis, visual field losses which are usually transient, but may be permanent, coma and death.

Other reactions: Headache, trembling, shaking, chills without fever and lightheadedness. Temporary renal shutdown or other nephropathy. (Adverse reactions to specific procedures receive comment under that procedure in the Dosage and Administration Section).

Post-Market Adverse Drug Reactions:

Endocrine disorders: Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to adult and pediatric patients, including infants. Some patients were treated for hypothyroidism

TREATMENT OF ADVERSE REACTIONS TO CONTRAST MEDIA

Contrast media should be administered only by physicians thoroughly familiar with the emergency treatment of all adverse reactions to contrast media. The assistance of other trained personnel such as cardiologists, internists and anesthetists is required in the management of severe reactions.

A guideline for the treatment of adverse reactions is presented below. This outline is not intended to be a complete manual on the treatment of adverse reactions to contrast media or on cardiopulmonary resuscitation. The physician should refer to the appropriate texts on the subject.

It is also realized that institutions or individual practitioners will already have appropriate systems in effect and that circumstances may dictate the use of additional or different measures.

For minor allergic reactions: (if considered necessary) the intravenous or intramuscular administration of an antihistamine such as diphenhydramine HCl 25-50 mg is generally sufficient (contraindicated in epileptics). The resulting drowsiness makes it imperative to ensure that out-patients do not drive or go home unaccompanied.

Major or life-threatening reactions: A major reaction may be manifested by signs and symptoms of cardiovascular collapse, severe respiratory difficulty and nervous system dysfunction. Convulsions, coma and cardiorespiratory arrest may ensue.

The following measures should be considered:

1. Start emergency therapy immediately - carefully monitoring vital signs.

2. Have emergency resuscitation team summoned - do not leave patient unattended.

3. Ensure patent airway - guard against aspiration.

4. Commence artificial respiration if patient is not breathing.

5. Administer oxygen if necessary.

6. Start external cardiac massage in the event of cardiac arrest.

7. Establish route for (intravenous (i.v.) medication by starting infusion of appropriate solution (5% dextrose in water).

8. Judiciously administer specific drug therapy as indicated by the type and severity of the reaction. Careful monitoring is mandatory to detect adverse reactions of all drugs administered:

    a) Soluble hydrocortisone 500-1000 mg i.v. for all acute allergic anaphylactic reactions.

    b) Adrenaline 1:1000 solution (in the presence of anoxia it may cause ventricular fibrillation):
        i) 0.2-0.4 mL subcutaneously for severe allergic reactions
        ii) in extreme emergency 0.1 mL per minute, appropriately diluted, may be given intravenously until desired effect is obtained. Do not exceed 0.4 mL.
        iii) in case of cardiac arrest 0.1-0.2 mL, appropriately diluted, may be given intracardially.

    c) In hypotension (carefully monitoring blood pressure):
        i) Phenylephrine HC1 0.1-0.5 mg appropriately diluted slowly i.v. or by slow infusion
        OR
        ii) Levarterenol bitartrate 4 mL of 0.2% solution in 1000 mL of 5% dextrose by slow drip infusion.

    d) Sodium bicarbonate 5%; 50 mL i.v. every 10 minutes as needed to combat post-arrest acidosis.

    e) Atropine 0.4-0.6 mg i.v. to increase heart rate in sinus bradycardia. May reverse 2nd or 3rd degree block.

    f) To control convulsions:
        i) Pentobarbital sodium 50 mg in fractional doses slowly i.v. (contra-indicated if cyanosis is present)
        OR
        ii) Diazepam 5-10 mg slowly i.v. titrating the dose to the response of the patient.

9. Defibrillation, administration of antiarrhythmics and additional emergency measures and drugs may be required.

10. Transfer patient to intensive care unit when feasible for further monitoring and treatment.

DOSAGE AND ADMINISTRATION

INTRAVENOUS INFUSION UROGRAPHY (Conray 30 and 43)

Intravenous infusion urography enhances the potential for more diagnostic information in those patients in whom the usual intravenous pyelography technique has not provided satisfactory visualization, or in those patients in whom there is reason to believe the usual intravenous pyelography technique will not provide satisfactory visualization. If renal function is not seriously impaired, the infusion urography technique usually provides satisfactory visualization of an unobstructed urinary tract, including nephrogram and cystogram. Additional advantages are the lack of necessity for dehydration of the patients and compression techniques.

Patient Preparation

For urography study, appropriate preparation of the patient is important for optimal visualization. A low residue diet is recommended on the day preceding the examination. Dehydration is not indicated for the performance of infusion urography. Patients should be maintained in an optimal state of hydration prior to the procedure. Unless contraindicated, a laxative may be given the evening before examination.

A preliminary radiograph usually is made prior to infusion of the contrast agent.

Precautions

A definite risk is involved in intravenous infusion urography in patients known to have chronic renal disease or multiple myeloma. This risk is not a contraindication to the procedure. However, partial dehydration in preparation of these patients is not recommended.

In addition to the general precautions previously described, infants and small children should not have any fluid restrictions prior to intravenous infusion urography. Injections of Conray represent an osmotic load which, if superimposed on increased serum osmolality due to partial dehydration, may magnify hypertonic dehydration. Intravenous infusion urography in diabetic patients may involve increased risks and partial dehydration in these patients is not recommended (see also General Precaution Section).

Patients with severely impaired renal function should be maintained in an appropriate state of hydration before the procedure. The increased osmotic load associated with intravenous infusion urography should be considered in patients with congestive heart failure.

Dosage and Administration
It is advisable that Conray be at or close to body temperature when infused.

Conray 30
The recommended dose for adults, older children and infants is 2-4 mL/kg with a maximum not exceeding 300 mL in adults and a proportionally smaller amount in children according to age and weight.

The solution is injected through an appropriate i.v. needle at a rate of approximately 50 mL per minute. Any appropriate intravenous administration set may be used observing the usual precautions for maintaining sterility and safety in administration. Films are usually taken at 5 minute intervals following the initiation of the infusion for a total of 20 minutes.

In patients with impaired renal function, diagnostic opacification frequently is achieved only after prolonged periods. In these individuals, periodic film obtained up to 24 hours after infusion might yield useful information.

Special procedures such as nephrotomography and cystography are best accomplished within 30 minutes of the conclusion of the infusion.

Conray 43
The usual dose in adults and children is 2-3 mL/kg by intravenous administration, not to exceed a total dose of 200 mL in adults and a proportionally smaller amount in children according to age and weight.

The solution is infused at a rate of approximately 40-50 mL per minute. Other infusion details are as for Conray 30.

CONTRAST ENHANCEMENT OF COMPUTED TOMOGRAPHIC (CT) BRAIN IMAGING

Tumours
Conray may be useful to enhance the demonstration of 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; craniopharyngiomas; germinomas; and metastatic

lesions.

The usefulness of contrast enhancement for the investigation of the retrobulbar space and in cases of low grade or infiltrative glioma has not been demonstrated.
Maximum contrast enhancement frequently occurs at a time following peak blood iodine concentration. This delay in maximum contrast enhancement can range from five to forty minutes, depending on the peak blood iodine concentration achieved (total dose and rate of administration) and the cell type of the tumour.

In cases where lesions have calcified, there is less likelihood of enhancement. Following therapy, tumours may show decreased or no enhancement.

Non-Neoplastic Conditions
The use of Conray may be beneficial in the image enhancement of non-neoplastic lesions. Cerebral infarctions of recent onset may be better visualized with the contrast enhancement while some infarctions are obscured if contrast media are used. The use of Conray resulted in contrast enhancement in 60% of cerebral infarctions studied from one week to four weeks from the onset of symptoms.

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

Arteriovenous malformations and aneurysms usually show contrast enhancement. In the case of 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 case of intraparenchymal clot, for which there is no obvious clinical explanation, contrast medium administration may be helpful in ruling out the possibility of associated arteriovenous malformation.

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

Patient Preparation
No special patient preparation is required for contrast enhancement of CT brain scanning. However, it is advisable to ensure that patients are well hydrated prior to examination.

Warning
Convulsions have occurred in patients with primary or metastatic cerebral lesions following the administration of iodine containing radiopaque media for the contrast enhancement of CT brain

images.

Dosage and Administration

Conray 60

The recommended dose of Conray 60 for adults and children is 1-2 mL/kg of body weight, not exceeding 150 mL in adults and proportionally smaller amount in children according to age and weight. In most cases, scanning may be performed immediately after completion of administration; however when fast scanning equipment (less than 1 minute) is used consideration should be given to waiting approximately 5 minutes to allow for maximum contrast enhancement of the neoplasm (tumour).

Conray 43

The usual dose in adults and children is 2-3 mL/kg by intravenous administration, not to exceed a total dose of 200 mL in adults and a proportionally smaller amount in children according to age and weight. In most cases, scanning may be performed immediately after completion of administration; however when fast scanning equipment (less than 1 minute) is used consideration should be given to waiting approximately 5 minutes to allow for maximum contrast enhancement.

Conray 30

The recommended dose for adults and children is 2-4 mL/kg, not exceeding 300 mL in adults and proportionately smaller amount in children according to age and weight. The dose should be infused as rapidly as possible through any well vented intravenous administration set and needle, observing the usual precautions for maintaining sterility.

CRANIAL COMPUTED ANGIOTOMOGRAPHY (Conray 60)

Conray 60 may be administered by intravenous bolus injection, or by bolus injection followed by rapid infusion.

For bolus injection, the usual dose in adults and children is 1 mL/kg at an injection rate of 2 mL/second with scanning begun immediately after administration.

This dose may be repeated as necessary. The total dose per procedure should not exceed 200 mL in adults and in children the total dose is reduced in approximate proportion to age and body weight.

In adults, when the rapid, high dose combination bolus and infusion technique is used, a 50 mL bolus injection followed by a rapid infusion of 150 mL may be given or a 100 mL bolus injection followed by a rapid infusion of 100 mL may be used. Scanning is begun immediately after the bolus administration. In children, the dose is reduced in approximate proportion to age and body

weight.

COMPUTED TOMOGRAPHY OF THE BODY (Conray 60)

Conray 60 may be administered when necessary to visualize vessels and organs in patients undergoing CT of the chest, abdomen and pelvis.

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

Continuous or multiple scans separated by intervals of 1-3 seconds during the first 30-90 seconds post-injection of the contrast medium (dynamic CT scanning) provide enhancement of diagnostic significance. Subsets of patients in whom delayed body CT scans might be helpful have not been identified. Inconsistent results have been reported and abnormal and normal tissues are usually isodense during the time frame used for delayed CT scanning. The risks of such indiscriminate use of contrast media are well known and such use is not recommended. At present, consistent results have been documented using dynamic CT techniques only.

Precautions

In addition to the general precautions previously described, it should be noted that patient motion, including respiration, can markedly effect image quality, therefore, patient cooperation is essential. The use of an intravascular contrast medium can obscure tumors in patients undergoing CT evaluation of the liver resulting in a false negative diagnosis (see Pharmacology section.)

Patient Preparation

No special patient preparation is required for contrast enhancement in computerized tomography. However, it is advisable to insure that patients are well hydrated prior to examination.
In patients undergoing abdominal or pelvic examination, opacification of the bowel may be valuable in scan interpretation.

Usual Dosage

Conray 60 may be administered by bolus injection, by rapid infusion or by a combination of both.

For vascular opacification, a bolus injection of 25-50 mL may be used, repeated as necessary. When prolonged arterial or venous phase enhancement is required and for the enhancement of specific lesions, a rapid infusion of 150 mL may be used. In some instances, a 100-150 mL infusion may be employed to define the area of interest followed by bolus injections of 20-50 mL

to clarify selected scans.

EXCRETORY UROGRAPHY (Conray 60)

Following intravenous injection, Conray is rapidly excreted by the kidneys. Conray may be visualized in the renal parenchyma 30 seconds following bolus injection. Maximum radiographic density of the calyces and pelves occurs in most instances about 3-8 minutes after injection. In patients with severe renal impairment, contrast visualization may be substantially delayed, or opacification may not occur at all.

Patient Preparation
Appropriate preparation of the patient is important for optimal visualization. A low residue diet is recommended for the day preceding the examination and a laxative is given the evening before the examination, unless contraindicated. A preliminary radiograph is usually made prior to the injection of the contrast agent.

Precautions
In addition to the general precautions previously described, infants and small children should not have any fluid restrictions prior to excretory urography. Injections of Conray represent an osmotic load which, if superimposed on increased serum osmolality due to partial dehydration, may magnify hypertonic dehydration. Therefore, patients' state of dehydration should be evaluated prior to and following this procedure and adjusted if necessary.

A definite risk is involved in excretory urography in patients known to have chronic renal disease multiple myeloma or diabetes. This risk is not a contraindication to the procedure (see WARNINGS and PRECAUTIONS, General concerning preparatory dehydration).

Usual Dosage (Conray 60)
Adults - The usual dose is 30-60 mL. Children 14 years of age and over, of average weight, may receive the adult dose.The total dose is normally injected within 30-90 seconds. The higher dosage may be indicated to achieve optimum results in instances where poor visualization may be anticipated. When nephrograms and/or sequential urograms are desired, the total dose should be rapidly injected, normally within 15-30 seconds.

The dosage for children is reduced in proportion to age and body weight. The following approximate schedule is recommended for infants and children based on a dosage of about 0.5 mL/kg of body weight:

Under 6 months of age	5 mL
6 - 12 months	8 mL

1 - 2 years	10 mL
2 - 5 years	12 mL
5 - 8 years	15 mL
8 - 12 years	18 mL
12 - 14 years	20-30 mL

CEREBRAL ANGIOGRAPHY(Conray 60)

Conray 60 may be used to visualize the cerebral vasculature by any of the accepted techniques, including digital subtraction angiography.

Patient Preparation
Cerebral angiography is normally performed with local or general anesthesia (see Precautions, General.) Premedication may be employed as indicated.

A preliminary radiograph is usually made prior to injection of the contrast agent.

Precautions
In addition to the general precautions previously described, cerebral angiography should be performed with special caution in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism and migraine.

Adverse Reactions
In addition to the general adverse reactions previously described, the major sources of cerebral arteriographic adverse reactions appear to be related to repeated injections of the contrast material, administration of doses higher than those recommended, the presence of occlusive atherosclerotic vascular disease and the method and technique of injection.

Adverse reactions are normally mild and transient. A feeling of warmth in the face and neck is frequently experienced. Infrequently, a more severe burning discomfort is observed.

Serious neurological reactions that have been associated with cerebral angiography include stroke, amnesia, respiratory difficulties, hemiparesis, visual field loss, aphasia, convulsions, hypotension, bradycardia, coma and death.

Usual Dosage
The usual dosage employed varies with the site and method of injection and the age, condition and weight of the patient. In adults, carotid and vertebral angiography, by either the percutaneous needle or catheter methods, is usually performed with a single rapid injection of 6-10 mL. Additional injections are made as indicated. Retrograde brachial cerebral angiography,

in adults, is usually performed with a single rapid injection of 35-50 mL into the right brachial artery. Other dosages may be employed depending upon the vessel injected and the procedure followed. The dose for children is reduced in approximate proportion to age and body weight.

The use of an arterial digital subtraction technique allows the dose (concentration and/or volume) of the contrast material to be reduced by approximately 50% and permits less selective arterial catheterization.

PERIPHERAL ARTERIOGRAPHY AND VENOGRAPHY

Conray may be injected to visualize the arterial and venous peripheral circulation. Arteriograms of the upper and lower extremities may be obtained by any of the established techniques. Most frequently, a percutaneous injection is made into the brachial artery in the arm or the femoral artery in the leg. Venograms are obtained by injection into an appropriate vein in the upper and lower extremity.

Patient Preparation

The procedure is normally performed with local or general anesthesia (see Precautions, General). Premedication may be employed as indicated. A preliminary radiograph is usually made prior to the injection of the contrast agent.

Precautions

In addition to the general precautions previously described, moderate decreases in blood pressure occur frequently with intra-arterial (brachial) injections. This change is usually transient and requires no treatment; however, the blood pressure should be monitored for approximately ten minutes following injection. Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In the presence of venous stasis, vein irrigation with normal saline should be considered following the procedure.

Adverse Reactions

In addition to the general adverse reactions previously described, hemorrhage and thrombosis have occurred at the puncture site of the percutaneous injection. Brachial plexus injury has been reported following axillary artery injection. Thrombophlebitis, syncope and very rare cases of gangrene have been reported following venography.

Usual Dosage

Peripheral Arteriography: In adults, a single rapid injection of 20-40 mL is normally sufficient to visualize the entire extremity. The dose for children is reduced in proportion to body weight.

The use of an arterial digital subtraction technique allows the dose (concentration and/or volume) of the contrast material to be reduced by approximately 50% and permits less selective arterial catheterization.

Venography: The usual dose of Conray 60 for adults is a single rapid injection of 20-40 mL. The dose for children is reduced in proportion to body weight.

The usual dose of Conray 43 is 30 mL single dose up to a cumulative total dose of 125 mL per lower extremity, depending on the technique used. The dose for children is reduced in proportion to body weight. Following the procedure the venous system should be flushed with either 5% dextrose in water (D5W) or normal saline (Sodium Chloride Injection USP), or the contrast medium should be removed by leg massage and/or leg elevation.

ARTHROGRAPHY (Conray 60)

Precautions

In addition to the general precautions previously described, strict aseptic technique is required to prevent the introduction of infection. Fluoroscopic control should be used to ensure proper introduction of the needle into the synovial space and prevent extracapsular injection. Aspiration of excessive synovial fluid will reduce the pain on injection and prevent the rapid dilution of the contrast agent. It is important that undue pressures not be exerted during the injection.

Adverse Reactions

In addition to the general adverse reactions previously described, arthrographymay induce joint pain or discomfort which is usually mild and transient but occasionally may be severe and persist for 24 to 48 hours following the procedure. Effusion requiring aspiration may occur in patients with rheumatoid arthritis.

Usual Dosage

Arthrography is usually performed under local anesthesia. The amount of contrast agent required is solely dependent on the size of the joint to be injected and the technique employed.

The following dosage schedule for normal adult joints should serve only as a guide since joints may require more or less contrast medium for optimal visualization. Dosage should be reduced for children in proportion to body weight.

knee, hip	5-15 mL
shoulder, ankle	5-10 mL
other	1- 4 mL

Passive or active manipulation is used to disperse the medium throughout the joint space.

The lower volumes of contrast medium are usually employed for double contrast examinations. Following the injection of the contrast medium 50-100 cc of either filtered room air or carbon dioxide is introduced for examination of the knee and lesser volumes for other joints.

DIRECT CHOLANGIOGRAPHY (Conray 60)

Precautions

In addition to the general precautions previously described, percutaneous transhepatic cholangiography should only be attempted when compatible blood for potential transfusions is in readiness and emergency surgical facilities are available.

The patient should be carefully monitored for at least 24 hours to ensure prompt detection of bile leakage and hemorrhage. Appropriate premedication of the patient is recommended and drugs which are cholespastic, such as morphine, should be avoided. Respiratory movements should be controlled during introduction of the needle.

Adverse Reactions

In addition to the general adverse reactions previously described, adverse reactions may often be attributed to injection pressure or excessive volume of the medium resulting in overdistention of the ducts and producing local pain.

Some of the medium may enter the pancreatic duct which may result in pancreatic irritation. Occasionally, nausea, vomiting, fever, and tachycardia have been observed. Pancholangitis resulting in liver abscess or septicemia has been reported.

In percutaneous transhepatic cholangiography, some discomfort is common, but severe pain is unusual. Complications of the procedure are often serious and have been reported in 4 to 5 percent of patients. These reactions have included bile leakage and biliary peritonitis, gallbladder perforation, internal bleeding (sometimes massive), blood-bile fistula resulting in septicemia involving gram-negative organisms, and tension pneumothorax from inadvertent puncture of the diaphragm or lung. Bile leakage is more likely to occur in patients with obstructions that cause unrelieved high biliary pressure.

Dosage and Administration

It is advisable that Conray 60 be at or close to body temperature when injected. The injection is made slowly without undue pressure, taking the necessary precautions to avoid the introduction of bubbles.

Operative Cholangiography - The usual dose is 10 mL but as much as 25 mL may be needed depending upon the caliber of the ducts. If desired, the contrast agent may be diluted 1:1 with Sodium Chloride Injection USP using strict aseptic procedures. Following surgical exploration of the ductal system, repeat studies may be performed before closure of the abdomen using the same dose as before.

Postoperative Cholangiography - Postoperatively, under fluoroscopic control, the ductal system may be examined by injection of the contrast agent through an in-place T-Tube. These delayed cholangiograms are usually made from the fifth to the tenth postoperative day prior to removal of the T-Tube. The usual dose is the same as for operative cholangiography.

Percutaneous Transhepatic Cholangiography - This procedure is recommended for carefully selected patients only for the diagnosis of jaundice in suspected extrahepatic biliary obstruction. The procedure is only employed where oral or intravenous cholangiography and other procedures have failed to provide the necessary information. In obstructed cases, percutaneous transhepatic cholangiography is used to determine the cause and site of obstruction to help plan surgery. The technique may also be of value in avoiding laparotomy in poor risk jaundice patients since failure to enter a duct by an experienced physician is considered to be suggestive of obstructive jaundice. Careful attention to technique is essential for the success and safety of the procedure. The procedure is performed under fluoroscopic control; local anesthesia following analgesic premedication is usually employed.

Depending upon the caliber of the biliary tree, a dose of 10 to 40 mL is generally sufficient to opacify the entire ductal system. If desired, the contrast agent may be diluted 1:1 with Sodium Chloride Injection USP using strict aseptic procedures.

As the needle is advanced or withdrawn, a bile duct may be located by frequent aspiration for bile or mucus. Before the dose is administered, as much bile as possible is aspirated. The injection may be repeated for exposures in different planes and repositioning of the patient, if necessary, should be done with care. If a duct is not readily located by aspiration, successive small doses of 1 to 2 mL of the medium are injected into the liver as the needle is gradually withdrawn, until a duct is visualized by X-ray. If no duct can be located after 3 or 4 attempts, the procedure should be terminated. Inability to enter a duct by a person experienced in the technique is generally considered to be suggestive of obstructive disease.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (Conray 60)

Endoscopic retrograde cholangiopancreatography (ERCP) is indicated in carefully selected patients with known or suspected pancreatic or biliary tract disease when other diagnostic procedures have failed to provide the necessary diagnostic information. Prior to the development

of ERCP, X-ray examination of the pancreatic ducts could only be obtained at laparotomy.

Precautions
Endoscopic retrograde cholangiopancreatography should only be performed by personnel skilled and experienced with the procedure, and careful attention to technique is essential for the success and safety of the procedure. Fluoroscopy is mandatory during injection to prevent over distention of the duct systems.

Filling of the pancreatic parenchyma must be avoided. Retrograde injection of contrast media beyond a significant stenosis or obstruction is not recommended, since this is considered to increase the risk of ascending infection. ERCP should not be performed in patients with a positive test for Hepatitis Associated Antigen, since fiberscopes cannot be sterilized and there is a real possibility of transmitting viral hepatitis to successive patients.

Adverse Reactions
Adverse reactions that have occurred and attributable to either the procedure or contrast agent include nausea, vomiting, fever, severe abdominal pain, duodenal wall intravasation, septicemia, pancreatitis, and perforation of the common bile duct associated with pathology. Frequently, elevation of serum amylase is observed following an ERCP procedure.

Dosage and Administration
The procedure is usually performed following pharyngeal anesthesia and analgesic or sedative premedication. Duodenal motility may be controlled in patients with active duodenal peristalsis with an appropriate antiperistaltic agent.

The contrast medium should be injected slowly without undue pressure under fluoroscopic control employing the minimal dose that is adequate to visualize the common bile duct, the pancreatic duct, or both duct systems. When both systems are filled simultaneously, overfilling of the pancreas is a potential risk. The dosage will vary greatly depending on the pathological findings and can range from 10-40 mL for visualization of the common bile duct, and from 2-10 mL for visualization of the pancreatic duct. Following the procedure, the patient should be kept under close observation for 24 hours.

INTRAVENOUS DIGITAL SUBTRACTION ANGIOGRAPHY (Conray 60)

Intravenous digital subtraction angiography (IV DSA) is a radiographic modality which allows dynamic imaging of the arterial system following intravenous injection of iodinated X-ray contrast media through the use of image intensification, enhancement of the iodine signal and digital processing of the image data. Temporal subtraction of the images obtained during the "first arterial pass" of the injected contrast medium injection yield images which are devoid of

bone and soft tissue.

Areas that have been examined by intravenous DSA are the heart, including coronary by-pass grafts; the pulmonary arteries; the arteries of the brachiophalic circulation; the aortic arch; the abdominal aorta and its major branches including the celiac, mesenterics and renal arteries; the iliac arteries; and the arteries of the extremities.

Patient Preparation
No special patient preparation is required for intravenous digital subtraction angiography. However, it is advisable to ensure that patients are well hydrated prior to examination.

Warnings
Convulsions have occurred in patients with primary or metastatic cerebral lesions following the administration of iodine containing radiopaque media for the contrast enhancement of CT brain images.

Patients with diabetes mellitus and impaired renal function are considered to be at greater risk to develop acute renal failure following the injection of large doses of contrast media for contrast enhancement in CT scanning.

Precautions
In addition to the general precautions previously described, the risks associated with IV DSA are those usually attendant with catheter procedures and include intramural injections, vessel dissection/rupture and tissue extravasation. Small test injections of contrast medium made under fluoroscopic observation to ensure the catheter tip is properly positioned, and in the case of peripheral placement that the vein is of adequate size, will reduce the potential for intramural injections, vessel dissection or tissue extravasation occurring.

Patient motion, including respiration and swallowing, can result in marked image degradation yielding non-diagnostic studies. Therefore, patient cooperation is essential.

Usual Dosage
Conray 60 may be injected either centrally, into the superior or inferior vena cava, or peripherally into an appropriate arm vein. For central injections, catheters may be introduced at the antecubital fossa into either the basilic or cephalic vein or at the leg into the femoral vein and advanced to the distal segment of the corresponding vena cava. For peripheral injections, the catheter is introduced at the antecubital fossa into an appropriate size arm vein. In order to reduce the potential for extravasation during peripheral injection, a catheter of approximately 20 cm in length should be employed.

Depending on the area to be imaged, the usual adult dose range is 20-60 mL. Injections may be repeated as necessary.

Central catheter injections are usually made with a power injection rate of between 10 and 30 mL/second. When making peripheral injections, rates of 12 to 20 mL/second should be used, depending on the size of the vein. Also, since contrast medium may remain in the arm vein for an extended period following injection, it may be advisable to flush the vein, immediately following injection with an appropriate volume (20-25 mL) or 5% Dextrose in water or normal saline.

OVERDOSAGE

Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. The symptoms may include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma and cardiac arrest. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of specific therapy. Iothalamate salts are dialyzable.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Following intravascular injection, Conray is rapidly transported through the circulatory system to the kidneys and is excreted unchanged in the urine by glomerular filtration. Renal accumulation is sufficiently rapid that maximum radiographic density in the calyces and pelves occurs in most instances about 3-8 minutes after injection. In patients with impaired renal function, diagnostic opacification frequently is achieved only after prolonged periods.

Angiography may be performed following intravascular injection of Conray which will permit visualization until significant hemodilution occurs.

The biliary system, pancreatic duct or joint spaces may be visualized by injecting the contrast medium directly into the region to be studied.

Injectable iodinated contrast agents are excreted either through the kidneys or through the liver. These two excretory pathways are not mutually exclusive, but the main route of excretion seems

to be related to the affinity of the contrast medium for serum albumin. Iothalamate salts are poorly bound to serum albumin, and are excreted mainly through the kidneys.

The liver and small intestine provide the major alternate route of excretion. In patients with severe renal impairment, the excretion of this contrast medium through the gall bladder and into the small intestine sharply increases.

Iothalamate salts cross the placental barrier in humans and are excreted unchanged in human milk.

Computerized Tomography of the Head

When Conray 60, 43 or 30 is used for contrast enhancement in computed tomographic brain scanning; the degree of enhancement is directly related to the amount of iodine administered. Rapid infusion of the entire dose amount yields peak blood iodine concentrations immediately following the infusion, which fall rapidly over the next 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 by about ten minutes; thereafter, the fall becomes exponential. With respect to tumours, maximum contrast enhancement frequently occurs at a time following peak blood iodine concentration.

This delay in maximum contrast enhancement can range from five to forty minutes, depending on the peak iodine levels achieved and the cell type and vascularity of the tumour. This lag suggests that the contrast enhancement of the image is at least in part dependent on the passage of iodine through the defective blood-brain barrier and on its accumulation within the lesion and outside the blood pool. The image enhancement of non-tumoral lesions, such as arteriovenous malformations and aneurysms, is probably dependent on the iodine content of the circulating blood pool. Studies indicate that equilibrated blood iodine levels of 100 mg% are required in most cases to achieve adequate contrast enhancement. This can be accomplished by the infusion of approximately 30 to 40 grams of iodine (100 to 150 mL of Conray 60 or 200 to 300 mL of Conray 30).

In brain scanning, the contrast medium does not accumulate in normal brain tissue due to the presence of the "blood brain barrier". The increase in X-ray absorption in the normal brain is due to the presence of the contrast agent within the blood pool. A break in the blood brain barrier, such as occurs in malignant tumours of the brain, allows accumulation of the contrast medium within the interstitial tumour tissue; adjacent normal brain tissue does not contain the contrast medium. When used for cranial computerized angiotomography, rapid bolus injection and/or infusion combined with rapid CT scanning will provide clear delineation of the cerebral vessels.

Computerized Tomography of the Body

In non-neural tissues (during CT of the body), Conray diffuses rapidly from the vascular to the extra-vascular 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 since no barrier exists; contrast enhancement is thus due to the relative differences in extra-vascular diffusion between normal and abnormal tissue, quite different from that in the brain.

Enhancement of CT with Conray 60 may be of benefit in establishing diagnoses of certain lesions in some sites with greater assurance than is possible with unenhanced CT and in supplying additional features of the lesions. In other cases, the contrast medium may allow visualization of lesions not seen with CT alone or may help to define suspicious lesions seen with unenhanced CT.

The pharmacokinetics of Conray in normal and abnormal tissue has been shown to be variable. Contrast enhancement appears to be greatest within 30-90 seconds after bolus administration, thus greatest enhancement can be detected by a series of consecutive 2-3 second scans ("Dynamic CT Scanning") during this time period. Dynamic scanning may improve enhancement and diagnostic assessment of tumours and other lesions such as an abscess, occasionally revealing more extensive disease. A cyst, or similar non-vascularized lesions may be distinguished from vascularized solid lesions by comparing enhanced and unenhanced scans; the vascularized lesions would show an increase. The latter might be benign, malignant or normal, but it is unlikely that it would be a cyst, hematoma or other non-vascularized lesion.

Venography

Venography may be performed with Conray 43 or 60 following injection into an appropriate vein and will permit visualization until sufficient hemodilution occurs.

STORAGE AND STABILITY

Store between 15-30°C. Protect from light and freezing. Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Conray 60 contains in each millilitre: 600 mg iothalamate meglumine, 0.09 mg edetate calcium disodium as a stabilizer and 0.125 mg of monobasic sodium phosphate as a buffer, and provides

28.2% (282 mg/mL) organically bound iodine. Conray 60 is available 30, 50, 100 and 150 mL bottles.

Conray 43 contains in each millilitre: 430 mg of iothalamate meglumine, 0.110 mg edetate calcium disodium and 0.110 mg of monobasic sodium phosphate as a buffer, and provides 20.2% (202 mg/mL) organically bound iodine. Conray 43 is available in 50 and 250 mL bottles.

Conray 30 contains in each millilitre: 300 mg of iothalamate meglumine, 0.11 mg edetate calcium disodium as a stabilizer and 0.125 mg of monobasic sodium phosphate as a buffer, and provides 14.15% (141 mg/mL) organically bound iodine. Conray 30 is available in 150 mL bottles.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

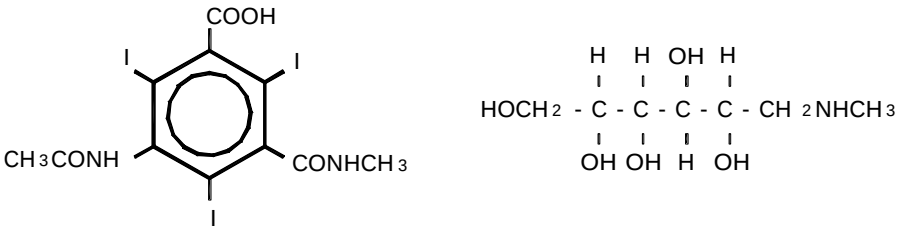
Drug Substance

Proper name: Iothalamate Meglumine Injection USP 30% w/v, 43% w/v and 60% w/v

Chemical name: N-methylglucamine salt of 5-acetamido-2,4,6 triiodo-N-methylisophthalamic acid

Molecular formula and molecular mass: $C_{11}H_9O_4N_2I3$, 613.94

Structural formula:



Physicochemical properties:

Conray is a sterile aqueous solution of iothalamate meglumine. The free acid contains 62% organically bound iodine.

Conray 60 has an osmolarity of approximately 1000 mOsm per litre, an osmolality of approximately 1400 mOsm per kilogram, and is therefore hypertonic under conditions of use. The osmolarity of Conray 43 is approximately 800 mOsm, the osmolality approximately 1000 mOsm per kilogram, and it is therefore hypertonic under conditions of use. Conray 30 has an osmolarity of approximately 750 mOsm per litre and is also hypertonic under conditions of use.

Conray 60 has a specific gravity of 1.32 at 25°C and a viscosity of 6 cps at 25°C and 4 cps at 37°C.Conray 43 has a specific specific gravity of 1.22 at 25°C and a viscosity of 3 cps at 25°C and 2 cps at 37°C.Conray 30 has a specific gravity of 1.16 at 25°C and the viscosity at 25°C is 2.0 cps and 1.5 cps at 37°C.

The above solutions are supplied in containers from which the air has been displaced by nitrogen. The solutions are clear, with no undissolved solids. Crystallization does not occur at normal room temperatures.

DETAILED PHARMACOLOGY

Excretion

Following intravenous administration, iothalamate meglumine is quickly transported to the kidneys where it is rapidly eliminated. Normally functioning kidneys begin to excrete the medium almost immediately. Maximum radiographic density in the kidney calyces and pelves occurs in most instances within three to eight minutes after injection. Dotter[1], et al. found that analysis of urine specimens collected one hour following the injection of Conray revealed that with normal renal function from one-third to one-half the injection iodine was excreted.

Kidney excretion studies in dogs revealed that the degree of visualization of the renal pelves, ureters, and bladder with iothalamate was excellent with most of the drug being eliminated within two hours.

Pharmacodynamics

The pharmacodynamics of iothalamate were studied by administering it intravenously to anaesthetized dogs at graded dosage levels ranging from 100 to 8,000 mg/kg of body weight. At all dosage levels, slight transient fluctuations in blood pressure were noted. In one dog, a moderate to marked increase in blood pressure was noted at levels above 1,000 mg/kg. Moderate respiratory stimulation was also noted at dosage levels greater than 1,000 mg/kg. The cardiac rate remained essentially unchanged at all levels and the electrocardiographic pattern was normal from 100-4,000 mg/kg.

Protein Binding and Effect on Whole Blood

Lasser[2] found that Conray possesses low protein binding characteristics and that whole blood incubations of 1:100 dilutions of the various radiopaque media reveal that Conray does not cause the red cell crenation seen with sodium acetrizoate nor the agglutination and rouleaux formation of diatrizoate meglumine.

TOXICOLOGY

Toxicity Studies [3, 4, 5, 6, 7, 8, 9, 10, 11]

Intravenous Administration: The acute intravenous toxicity of iothalamate meglumine has been determined in three separate studies in mice and in one study of rats. In order to achieve the acute lethal range in mice and rats, the total volume of undiluted iothalamate meglumine administered intravenously was almost equivalent to the estimated total blood volumes of these animals. The IV LD_{50} in mice ranged from 16,000 to 18,600 mg/Kg and in rats was 20,000 mg/kg with confidence limits up to 22,400 mg/kg. In both species, lethality was preceded by

clonic and tonic convulsions, urination and gasping. Deaths apparently resulted from respiratory arrest within five minutes after dosing. Reactions in surviving animals were dose-related and less severe, characterized primarily by minor convulsions at higher doses to transient hyperactivity at lower doses. In these animals, recovery was uneventful within two to three minutes after injection.

Ten dogs anaesthetized with pentobarbital were infused with Conray 30 (6 dogs) or diatrizoate meglumine 30% (4 dogs) at 1 mL/kg/min. The average lethal dose of Conray 30 was 28.67 gm/kg and for diatrizoate meglumine 30%, 16.56 gm/kg.

Because all dogs were anaesthetized, progressive signs of acute toxicity were not observed. However, death was apparently due to respiratory arrest with both agents in that spontaneous respiration ceased several minutes prior to cardiac arrest. The lesser toxicity of Conray 30 was evidenced by a more stable blood pressure and heart rate. Whereas cardiovascular deterioration began at 30-40 minutes following diatrizoate meglumine 30%, a similar response was not seen with Conray 30 until 55-60 minutes.

Ten repeated intravenous daily doses of iothalamate meglumine at dosage levels of 500, 2,000 and 4,000-6,000 mg/kg were administered to male and female rats. Growth and survival were comparable to that of control rats receiving daily intravenous doses of sterile physiological saline. Hematology, pathology, and organ weight data were also generally comparable to the results with the control rats.

Two groups of dogs received ten daily intravenous doses of iothalamate meglumine. One group received ten daily 500 mg/kg doses, the other group received 4,000 mg/kg for the first five days and 6,000 mg/kg on days six through ten. Iothalamate meglumine was well tolerated by the dogs, the only difference observed in comparison to a saline control group was the occurrence of some vomiting at the 4,000-6,000 mg/kg level.

Hematological and biochemical studies, urine analyses, and gross and microscopic pathological evaluations indicate essentially no differences between the dogs receiving iothalamate meglumine and the control animals.

Local irritation in the marginal ear veins of rabbits following ten daily intravenous injections of iothalamate meglumine was minimal and comparable to that observed with saline. The rabbits appeared normal throughout the experiment and gross necropsy was negative.

Intravenous administration of iothalamate meglumine to anaesthetized dogs was conducted at dosage levels ranging from 100 to 8,000 mg/kg. No serious adverse cardiovascular or respiratory effects were noted. The meglumine salt of iothalamic acid appeared to possess a

quantitatively greater hypotensive effect than the sodium salt.

Intracisternal Administration: Following the administration of iothalamate meglumine 60%, and diatrizoate meglumine 60% into the cisterna magna of male albino rabbits, it was determined that iothalamate meglumine is four times less toxic than its diatrizoate counterpart. Iothalamate meglumine had an approximate LD_{50} value of 78 mg/kg, while the meglumine salts of diatrizoate had a value of 20 mg/kg.

Teratology and Perinatal Weaning

Studies which were designed to determine any changes in the newborn (teratology) and in animals carried through weaning (perinatal), were conducted in mice and rats. These studies were carried out with iothalamate meglumine which was injected intraperitoneally, not intravenously, since the latter technique was not applicable to the study. Iothalamate meglumine was administered at doses of 1.44 and 5.76 gm/kg per day during an appropriate interval in the gestation period. No effects which differed from control findings were noted from iothalamate meglumine.

Neonatal Toxicity Studies

The comparative toxicity of iothalamate meglumine in adult versus neonatal rats was studied to determine the relative sensitivity of young versus mature animals. The results of these studies gave intravenous LD_{50} values of 24.65 gm/kg and 18.57 gm/kg for adults and neonates, respectively. Comparison of the LD_{50} values in rats suggests that the neonate is approximately 1.34 times more sensitive than the adult to the toxic effects of iothalamate meglumine.

Blood-Brain Barrier Studies - Dogs

Twenty-five dogs were injected with 25 mL each of contrast media solution into the right common carotid artery in 10 seconds. Following the intravenous infusion of Trypan blue dye, the brain was removed and examined for staining to determine the extent to which the contrast medium had increased the permeability of the blood-brain barrier. The media used were iothalamate meglumine 60% (14 dogs) and diatrizoate sodium 50% (11 dogs). The results were as follows:

Degree of Brain Staining

	None	Barely Perceptible	Faint	Distinct	Intense
Iothalamate meglumine 60%	4	3	6	1	-
Diatrizoate sodium 50%	-	-	2	3	6

In addition to brain-staining intensity comparisons, blood pressure, respiration, neuromuscular and EKG responses were considered in evaluating the compounds. During and immediately following the injection, strong contractions of the neck and thoracic muscles were observed in seven of the eleven dogs receiving diatrizoate sodium 50%. Nine of the eleven dogs exhibited clonicotonic convulsions for a period of approximately six minutes, following which it was noted that the dogs were hypersensitive to sound and touch. Moderate respiratory stimulation and appreciable changes in the EKG pattern were also observed.

Unlike the dogs receiving diatrizoate sodium 50%, none of the dogs receiving iothalamate meglumine 60% exhibited convulsions, nor was hypersensitivity to sound and touch noted. Four of these dogs exhibited slight to mild contractions of the neck and thoracic muscles, the remaining ten appeared to be unaffected by the procedure. There was no appreciable effect on the respiratory rate or arterial blood pressure, and only slight changes in the EKG pattern were noted.

REFERENCES

1. Dotter, C.T., Straube, K.R., Bilbao, M.K., and Hinck, V.C.: "New Contrast Medium for Intravascular Use", Northwest Medicine,. 61:41-6, (January) 1962.

2. Lasser, E.C., Farr, R.S., Fujimaqari, T., and Tripp, W.N.; "The Significance of Protein Binding of Contrast Media in Roentgen Diagnosis", American Journal of Roentgenology, Radium Therapy and Nuclear Medicine, 87:338-60, (February) 1962.

3. Kodama, J.K. et al "Iothalamate a New Intravascular Radiopaque Medium with Unusual Pharmacotoxic Inertness". Exper. & Molec. Path. 265-980, (Dec.) 1963.

4. Hilal, S.K. "Hemodynamic Changes Associates with the Intra-Arterial Injection of Contrast Media New Toxicity Tests and a New Experimental Contrast Medium". Radiology 86 (4): 615-633, (Apr.) 1966.

5. Foster, J.H. et al "Clinical Experiences with a New Angiographic Contrast Medium Sodium/Meglumine Iothalamate 78 Percent". Am. J. Roentgenol., 102: 451-454 (Feb.) 1968.

6. Melartin, E. et al "Neurtoxicity of Iothalamates and Diatrizoates: Significance of Concentration and Cation". Invest. Radiol., 5(1): 13-21, (Feb.) 1970.

7. Tuchimaa, P.J. and Melartin, E. "Neurotoxicity of Iothalamates and Diatrizoates: Historadioautographic Study of Rat Brains with 131Iodine-tagged Contrast Media". Invest. Radiol., 5 (1): 22-29, (Jan. - Feb.) 1970.

8. Rapoport, S.I. and Levitan, H. "Neurotoxicity of X-ray Contrast Media Relation to Lipid LSolubility and Blood-Brain Barrier Permeability". Am. J. Roentgenol., 122 186-193 (Sept.) 1974.

9. Dempsey, P.J., Goree, J.A. et al "The Effect of Contrast Media on Patient Motion During Cerebral Angiography". Radiology, 115: 207-209, (Apr.) 1975.

10. Shehadi, W.H. "Adverse Reactions to Intravascularly Administered Contrast Media, A Comprehensive Study Based on a Prospective Survey", Am. J. Roentgenol., 124: 145-152 (May) 1975.

11. Hila, S.K. et al "Effect of Isotonic Contrast Agents on Spinal Reflexes in the Cat", Radiology, 122: 149-155 (Jan.) 1977.

12. Hinck, V.C. and Dotter, C.T.: "Cerebral Angiography with 60 Percent CONRAY, Preliminary Report", Journal of Neurosurgery, 19: 312-3, (April) 1962.

13. Marshall, T.R. and Ling, J.T.: "Clinical Evaluation of Two Contrast Media: CONRAY and Angio-Conray", American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine. 89:432-31, (February) 1963.

14. Marshall, T.R. and Long, T.J.: "Clinical Evaluation of a New Contrast Medium for Excretory Urography", Southern Medical Journal, 56: 1424-27, (December) 1963.

15. Smolik, E. and Nash, F.: "Cerebral Angiography with a New Contrast Medium", Missouri Medicine, 863-866, (September) 1962.

16. Steinberg, I. and Evans, J.A.: "CONRAY: A new Cardiovascular and Urographic Contrast Medium", Radiology, 79:395-400.

17. Lindheimer, W.: "Infusion Urography as a Method for Improvement of the Visualization of the Kidneys and Urinary Tracts", Med. Klin., 63 (16): 611-615, 1968.

18. Sargent, E., Nicholas and Donaldson, Norton: Infusion Excretory Urography, J. Can. Assoc. Radiology, XVII: 434-441, (December) 1967.

19. Wendth, Arthur J.: "Drip Infusion Pyelography", Am. J. Roent., Rad. Therap. and Nuc. Med. XCV (2): 269-282, (October) 1965.

20. Zanca, P.: "Infusion and Pyelography in Infants and Children", Texas Medicine, 62 (7): 49-53, 1966.

21. Zanca, Peter, and Doyle, John L.: "Diagnostic Value of Drip Infusion Pyelography", Clinical Medicine, 75: 35-44, (April) 1968.

PATIENT MEDICATION INFORMATION

CONRAY® 30
(Iothalamate meglumine injection USP 30% w/v)

CONRAY® 43
(Iothalamate meglumine injection USP 43% w/v)

CONRAY® 60
(Iothalamate meglumine injection USP 60% w/v)

Read this carefully before you start taking Conray and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Conray.

What is Conray used for?
Conray:

- is for diagnostic use only and is used to help identify an illness.
- makes contrast in the body that is useful during a CT scan or another type of complex computerized x-ray called digital subtraction angiography.
- is used to better visualize the kidneys, bladder, biliary and urinary tracts, lesions in the brain, abnormal tissues in the body and blood vessels.
- is used in children and adults.

How does Conray work?
Conray is injected through your blood vessels and creates contrast in your body. This contrast between the various tissues in your body makes it easier for your doctor to make a diagnosis.

What are the ingredients in Conray?
Medicinal ingredients: Iothalamic acid.
Non-medicinal ingredients: Edetate Calcium Disodium USP, Meglumine USP, Monobasic Sodium phosphate USP.

Conray comes in the following dosage forms:
Bottles of Iothalamate Meglumine Injection USP 30% w/v, 43% w/v or 60% w/v

Do not use Conray if:

- You are hypersensitive to this drug or to any ingredient in the formulation or component of the container.

- You have a kidney disease leading to a low production of urine (anuria, oliguria).
- You have blood clotting problems.
- You have an inflamed pancreas or an infected bile duct.
- You have bleeding in your brain.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Conray. Talk about any health conditions or problems you may have, including if you:

- had a previous allergic reaction to contrast agent or have a history or family history of iodine sensitivity.
- have cancer or a tumor.
- have multiple myeloma (cancer of the plasma blood cells).
- have a rare tumour on your adrenal gland (pheochromocytoma).
- have a history of bronchial asthma.
- have diabetes.
- have sickle cell disease.
- have a kidney disease, liver or biliary disorders.
- have both liver and kidney problems
- have severe low blood pressure or congestive heart failure
- have a fever or endotoxins in your blood (infection)
- have levels of thyroid hormone that are too high (hyperthyroidism)
- had an injection of a contrast agent 24 hours before you are to take Conray.
- are pregnant or could be pregnant. If you need to take Conray during your pregnancy, your doctor will discuss the benefits and risks of giving it to you.
- are breastfeeding. It is not known if Conray is excreted in breast milk. You should bottle feed your baby for at least 24 hours after taking Conray.

Thyroid function

Contrast media containing iodine, such as Conray, may change thyroid activity in some patients, both in adults and infants. This may cause:

- Hypothyroidism (i.e. too little thyroid hormones in the blood)
- Or hyperthyroidism (i.e. too much thyroid hormones in the blood)

Thyroid function in infants

Contrast media containing iodine may cause hypothyroidism in infants, especially infants born too soon that:

- Can continue for several weeks to a month after treatment
- Can harm growth and development
- Can harm mental growth

- May require treatment
- Can cause symptoms such as:
    - Fatigue, shortness of breath, low heart rate
    - Reduced appetite, feeling cold, weight gain
    - Muscle stiffness

Contact your doctor if these symptoms happen to you or your infant.

Your doctor may order blood tests for your infant after treatment to follow thyroid hormone levels in the blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Conray:
Conray will always be used in a hospital or similar setting. It will only be administered to you under the supervision of a health professional skilled and experienced in the particular procedure to be performed.

Usual dose:
- Your doctor will determine the amount of Conray to be used.
- The dose administered will depend on your weight, your age and the procedure.
- You may need to eat certain foods the day before your examination.
- You may need to take a laxative the night before your examination.
- Depending on the procedure you will have, you may need to receive an anesthetic.
- You will receive Conray by injection into a blood vessel.

Overdose:
Overdose affects mainly the heart and the lungs and can be life-threatening. The symptoms of overdose may include bluish skin, abnormally slow heart and bleeding in the lungs, seizures, coma and heart attack.

If you think you have been given too much Conray, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using Conray?

These are not all the possible side effects you may feel when taking Conray. If you experience any side effects not listed here, contact your healthcare professional. Ask your healthcare

professional about the side effects that may occur depending on your type of procedure. Side effects may include:
Common side effects may include:

- Nausea, vomiting, facial flush and feeling of body warmth.

Uncommon side effects can include:

- Rash, dry mouth, sweat.
- Burning pain at the site of the injection
- Headache, shaking, chills.

Serious side effects and what to do about them		
Symptom/ Effect	Talk to your healthcare professional	
	Only if severe	In all cases
UNCOMMON • Lack of a sufficient amount of the thyroid hormone (known as hypothyroidism) • Severe allergic reaction including symptoms such as: rash, edema, asthmatic attack, labored breathing, coughing, choking, chest tightness, temporary cessation of breathing, bluish discoloration of the skin. • Cardiac reaction including symptoms such as decrease of blood pressure, formation of blood clots, abnormal heart beat. • Neurologic reaction including symptoms such as convulsion, language disorder, syncope, paralysis, transient visual loss, coma and death. • Kidney disease or damage.		□□

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html, for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at controlled room temperature. Protect from light and freezing. Discard unused portion. Keep out of reach and sight of children.

If you want more information about Conray:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-844-208-7620.

This leaflet was prepared by Liebel-Flarsheim Canada Inc.
Liebel-Flarsheim Canada Inc.
Pointe-Claire, Quebec, H9R 5H8
CANADA

Conray® 30 / 43 / 60 is a trademark of Guerbet.

Revised: December 27, 2017