RENO-DIP - diatrizoate meglumine injection, solution
Bracco Diagnostics Inc

NOT FOR INTRATHECAL USE

DESCRIPTION

Reno-DIP (Diatrizoate Meglumine Injection USP 30%) is a radiopaque contrast agent supplied as a sterile, aqueous solution for intravenous use, in 300 mL bottles. Each mL provides 300 mg diatrizoate meglumine; at manufacture, 0.4 mg edetate disodium sequestering agent is added per mL. The pH has been adjusted between 6.0 and 7.7 with meglumine and diatrizoic acid. Each mL of solution also contains approximately 0.049 mg (0.002 mEq) sodium and 141 mg organically bound iodine.

CLINICAL PHARMACOLOGY

Following intravenous administration, diatrizoate meglumine is rapidly transported through the blood-stream to the kidneys and is excreted unchanged in the urine by glomerular filtration. When urinary tract obstruction is severe enough to block glomerular filtration, the agent appears to be excreted by the tubular epithelium.

Diuresis commonly occurs, due primarily to the osmotic effects of the contrast agent.

Drip Infusion Pyelography

When a large volume of the contrast agent is administered in dilute form by intravenous drip infusion, the nephrographic phase of renal excretion is enhanced, and a dense, sustained nephrogram is usually obtained.

Following drip infusion of the contrast agent, the upper and lower urinary tract is opacified. Anatomically complete pyelograms and voiding cystograms may be obtained, and the entire course of the ureter may be seen in a single film. Filling defects may be visualized and the site of an obstruction may be clearly localized.

Renal accumulation is sufficiently rapid that optimal opacification of the kidney normally is reached by the time the infusion is completed, while filling of the collecting system is maximal within 20 or 30 minutes after the start of the infusion. Impairment of renal function commonly delays accumulation and excretion of the

contrast agent, so that opacification may be delayed until three or more hours after the infusion; with severe impairment adequate opacification may not occur.

Because transport of the contrast agent is slowed by renal dysfunction, the ischemic kidney of renal vascular hypertension may be distinguished from the normal kidney. Renal ischemia produces a nephrogram which is slower to appear, less dense, and sustained for a markedly prolonged period of time.

Computed Tomography

Reno-DIP enhances computed tomographic brain scanning 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 infusion 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 brain scanning, Reno-DIP (Diatrizoate Meglumine Injection USP 30%) 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 tumor tissue. Adjacent normal brain tissue does not contain the contrast medium.

In nonneural tissues (during computed tomography of the body), diatrizoate 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 tumor tissue 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 diatrizoate 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 intra-arterial 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 scanning.

Lower Extremity Venography

Following intravenous injection of Reno-DIP (Diatrizoate Meglumine Injection USP 30%) into a suitable plantar vein, the agent opacifies those vessels into which it is distributed, permitting visualization of deep and superficial veins in the lower extremities until hemodilution occurs.

INDICATIONS AND USAGE

Drip Infusion Pyelography

Reno-DIP is indicated for use in those patients in whom routine pyelography would not be expected to be, or has not been, satisfactory for diagnosis. It is not intended to replace retrograde pyelography where this procedure is indicated.

Computed Tomography

Reno-DIP (Diatrizoate Meglumine Injection USP 30%) is also indicated for radiographic contrast enhancement in computed tomography (CT) of the brain and body. Contrast enhancement may be advantageous in delineating or ruling out disease in suspicious areas which may otherwise not have been satisfactorily visualized.

Brain Tumors

Reno-DIP may be useful to demonstrate 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. In cases

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

Non-Neoplastic Conditions of The Brain

The use of Reno-DIP may be beneficial in the enhancement of images of lesions not due to neoplasms. Cerebral infarctions of recent onset may be better visualized with the contrast enhancement, while some infarctions are obscured if a contrast medium is used. The use of Reno-DIP (Diatrizoate Meglumine Injection USP 30%) improved the contrast enhancement in approximately 60 percent of cerebral infarctions studied from one week to four weeks from the onset of symptoms.

Sites of active infection also will produce contrast enhancement following contrast medium administration.

Arteriovenous malformations and aneurysms will 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 cases 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 diagnoses in a number of normal studies.

Body Scanning

Reno-DIP may be used for enhancement of computed tomographic scans performed for detection and evaluation of lesions in the liver, pancreas, kidneys, aorta, mediastinum, abdominal cavity, pelvis and retroperitoneal space.

Enhancement of computed tomography with Reno-DIP 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 60-90 seconds after bolus administration of the 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 pre-contrast and enhanced scans are compared; the non-perfused 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.

Lower Extremity Venography

Reno-DIP (Diatrizoate Meglumine Injection USP 30%) is also indicated for lower extremity venography.

CONTRAINDICATIONS

Reno-DIP is contraindicated for use in intrathecal procedures.

This preparation is contraindicated in patients with a hypersensitivity to salts of diatrizoic acid.

The administration of diatrizoate meglumine is contraindicated in patients with anuria.

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.

The possibility exists for inadvertent administration into the intrathecal space during epidural administrations. Therefore, epidural administration procedures, such as pain management catheter placement, should not be performed with use of this product.

General

A definite risk exists in the use of intravascular contrast agents in patients who are known to have multiple myeloma. In such instances there has been anuria 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 the causative factor. The risk in myelomatous patients is not a contraindication to the procedures; however, partial dehydration in the preparation of these patients for the examination is not recommended since this may predispose to the precipitation of myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing this effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before intravascular administration of a contrast agent.

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.

Diatrizoate meglumine should be used with extreme caution in patients with severe concomitant hepatic and renal disease, and those with severe hypertension or congestive heart failure.

Since iodine-containing contrast agents may alter the results of thyroid function tests dependent on iodine estimation, such tests, if indicated, should be performed prior to the administration of this preparation.

A history of sensitivity to iodine per se or to other contrast media is not an absolute contraindication to the use of diatrizoate meglumine, but calls for extreme caution in administration.

In patients with subarachnoid hemorrhage, a rare association between contrast administration and clinical deterioration, including convulsions and death, has been reported; therefore, administration of intravascular iodinated ionic contrast media in these patients should be undertaken with caution.

PRECAUTIONS

Diagnostic procedures which involve the use of radiopaque contrast agents 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 (see ADVERSE REACTIONS).

Severe, life-threatening reactions suggest hypersensitivity to the radiopaque agent, which has prompted the use of several pretesting methods, none of which can be relied upon to predict severe reactions. Many authorities question the value of any pretest. A history of bronchial asthma or allergy, a family history of allergy, or a previous reaction to a contrast agent warrant special attention. Such a history, by suggesting histamine sensitivity and a consequent proneness to reactions, may be more accurate than pretesting in predicting the likelihood of a reaction, although not necessarily the severity or type of reaction in the individual case.

The sensitivity test most often performed is the slow injection of 0.5 to 1 mL of the radiopaque medium, administered intravenously, prior to injection of the full diagnostic dose. It should be noted that the absence of a reaction to the test dose does not preclude the possibility of a reaction to the full diagnostic dose. If the test dose causes an untoward response of any kind, the necessity for continuing with the examination should be carefully reevaluated and, if it is deemed essential, the examination should be conducted with all possible caution. In rare instances reactions to the test dose itself may be extremely severe; therefore, close observation of the patient, and facilities for emergency treatment appear indicated.

The recommended rate of infusion should not be exceeded.

Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by urographic agents. Diagnostic infusion studies should therefore be postponed in any patient with a known or

suspected hepatic or biliary disorder who has recently taken a cholecystographic contrast agent.

The diuretic effect of the drip infusion procedure may hinder an assessment of residual urine in the bladder.

Consideration must be given to the functional ability of the kidneys before injecting diatrizoate meglumine. Adequate visualization may be difficult or impossible to attain in uremic patients or others with severely impaired renal function.

Acute renal failure has been reported with the use of contrast agents in patients with diabetic nephropathy and susceptible nondiabetic patients (often elderly with preexisting renal disease).

Contrast agents may interfere with some chemical determinations made on urine specimens; therefore, urine should be collected before administration of the contrast media or two or more days afterwards.

Caution should be exercised during lower extremity venography when thrombosis, phlebitis, total venous system obstruction, severe ischemia, or local infection is suspected. Extreme caution during injection of the agent is needed to avoid extravasation and fluoroscopy is recommended, particularly in patients with severe arterial or venous disease.

Usage In Pregnancy

The safety of diatrizoate meglumine for use during pregnancy has not been established; therefore, it should be used in pregnant patients only when, in the judgement of the physician, its use is deemed essential to the welfare of the patient.

ADVERSE REACTIONS

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 the procedure and/or the radiopaque medium, appropriate emergency facilities and well-trained personnel should be available to treat both conditions. Emergency facilities and personnel should remain available for 30 to 60 minutes following the procedure since severe delayed reactions have been known to occur.

Nausea, vomiting, flushing, or a generalized feeling of warmth are the reactions most frequently encountered with intravenous administration of contrast agents. Such symptoms as chills, fever, sweating, headache, dizziness, pallor, weakness, severe retching and choking, wheezing, a rise or fall in blood pressure, ventricular fibrillation, cardiac arrest, facial or conjunctival petechiae, urticaria,pruritus, rash, and other eruptions, edema, cramps, tremors, itching, sneezing, lacrimation, etc., may occur. Antihistaminic agents may be of benefit; rarely such reactions may be severe enough to require discontinuation of dosage. Pulmonary edema, spasm, seizures, hemiparesis, syncope, and impairment of vision have also occurred. Neutropenia may also occur.

Severe reactions which may require emergency measures may take the form of a cardiovascular reaction characterized by peripheral vasodilatation with resultant hypotension and reflex tachycardia, apnea, dyspnea, agitation, and confusion and cyanosis progressing to unconsciousness. Or, the histamine-liberating effect of these compounds may induce an allergic-like reaction which may range in severity from rhinitis or angioneurotic edema to laryngeal or bronchial spasm or anaphylactoid shock.

Temporary renal shutdown or other nephropathy may occur.

Although local tissue tolerance to diatrizoate meglumine is usually good, intravenous injection of the medium in a more concentrated formulation has produced a few instances of a burning or stingingsensation or numbness and of venospasm or venous pain, and partial collapse of the injected vein.

Although not reported as resulting following lower extremity venography with diatrizoate meglumine, conditions such as thrombophlebitis, and the rare possibility of gangrene, should be considered as potential adverse reactions.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Reno-DIP (Diatrizoate Meglumine Injection USP 30%) should be at body temperature when administered and may need to be warmed before use.

Drip Infusion Pyelography

While preparation of the patient is not essential for drip infusion pyelography, it is advocated by some investigators. If desired, adults and older children may be given a laxative the night before the examination and a low residue diet the day before, to clear the gastrointestinal tract. Clinicians who feel that partial dehydration enhances radiographic contrast recommend a low liquid intake for 12 hours prior to the procedure; however, adequate hydration has improved the quality of films for other investigators. Preparatory partial dehydration is not recommended in infants, young children, the elderly, or azotemic patients (especially those with polyuria, oliguria, diabetes, advanced vascular disease, or preexisting dehydration). The undesirable dehydration in these patients may be accentuated by the osmotic diuretic action of the medium.

In uremic patients partial dehydration is not necessary and maintenance of adequate fluid intake is particularly desirable.

Cleansing enemas are not recommended, since they may increase residual gas in the bowel.

The recommended dose is 2 mL per pound of body weight. The preparation is given by continuous intravenous infusion, over a period of 8 minutes or longer (see PRECAUTIONS), through a needle with a large bore, usually a 17- or 18-gauge needle. In older patients and in patients with known or suspected cardiac decompensation, a slower rate of infusion is probably wise.

If nausea or flushing occurs during administration, the infusion should be slowed or briefly interrupted.

Films are taken before the onset of the infusion and at the desired intervals following its completion. When renal function is normal, a nephrogram may be taken as soon as the infusion is completed, and films of the collecting system at 10 and 20 minutes thereafter. Voiding cystourethrograms are usually optimal at 20 minutes after the infusion is completed. In hypertensive patients, early minute sequence films may be taken during the course of infusion, in addition to subsequent pyelograms. In patients with renal dysfunction, optimal visualization is usually delayed, and the late films are taken as indicated.

The nephrogram obtained by the drip infusion procedure may be dense enough to obscure the pelvocalyceal system in some cases. The presence of gas in the bowel may hamper early visualization of the renal collecting system. Tomographic “cuts” may help to overcome such difficulties.

Nephrotomography may begin when the infusion is completed. The sustained contrast achieved by the drip infusion technique eliminates the need for precise timing and teamwork that is necessary with ordinary nephrotomography. Thus, if nephrograms taken after infusion of the medium suggest the need for sectional films, or if preselected tomographic“cuts” are not sufficient, additional tomograms may be obtained at once, and without repetition of dosage.

Computed Tomography

Brain Scanning

The suggested dose is 2 mL per pound of body weight by intravenous drip over a period of eight minutes or longer; scanning may be performed during administration and/or immediately afterwards.

Body Scanning

The usual adult dose is 300 mL administered by intravenous infusion over a period of approximately 20 minutes; 150 mL may be infused immediately prior to scanning, and the balance during scanning. Scanning may also be performed immediately following completion of infusion of the entire dose.

Gastrografin® (Diatrizoate Meglumine and Diatrizoate Sodium Solution USP), an oral radiopaque contrast agent, may be useful as an adjunct to the procedure.

Patient Preparation

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

Lower Extremity Venography

Appropriate premedication, which may include an analgesic, a barbiturate, or a tranquilizer may be administered prior to the examination.

Prior to the administration of the contrast agent, patients should be well hydrated and a preliminary radiograph taken. The patient should be placed on a tilt table, semi-erect (30° to 60°).

The usual dose per intravenous injection may range from 50 to 100 mL; the usual total dose per extremity ranges from 100 to 300 mL. The dose for children should be

reduced in proportion to body weight. The dose may be given as a bolus injection or by steady drip infusion. Radiographs are taken at the start of injection/infusion and periodically thereafter at the discretion of the radiologist.

Following the procedure, the contrast agent may be removed from the venous system by flushing with either Dextrose Injection USP 5% or Sodium Chloride Injection USP 0.9%, or by leg massage and/or leg elevation.

HOW SUPPLIED

Reno-DIP (Diatrizoate Meglumine Injection USP 30%) is available in packages of 10 single dose 300 mL bottles (NDC 0270-0809-75). An excess volume (1 mL) is available in each container for sensitivity testing.

Storage

The preparation should be protected from strong light and stored at 20-25°C (68-77°F) [See USP].

Manufactured for
Bracco Diagnostics Inc.
Princeton, NJ 08543
by SICOR Pharmaceuticals, Inc.
Irvine, CA 92618

Printed in USA
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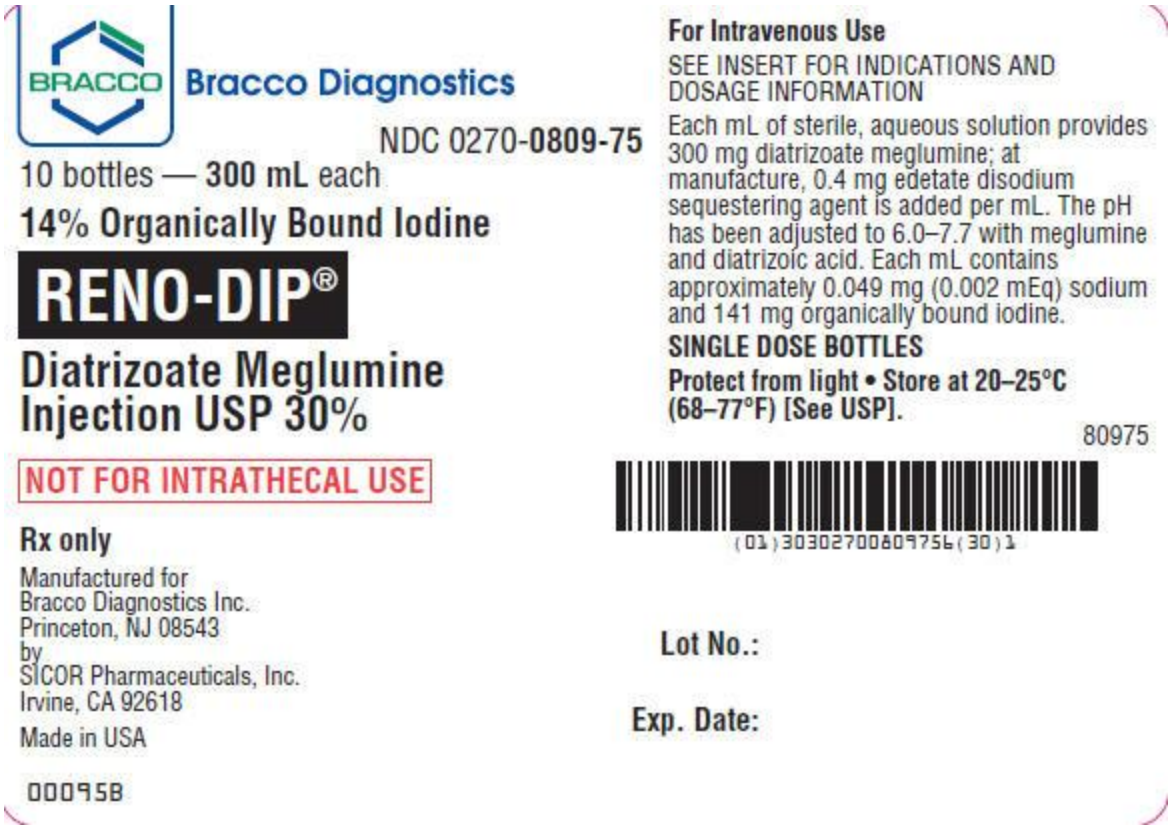
Reno-Dip® 10 Bottles 300 mL Label
NDC: 0809–75



RENO-DIP
diatrizoate meglumine injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0270-0809
Route of Administration	INTRAVENOUS	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
diatrizoate meglumine (diatrizoic acid)	diatrizoate meglumine	300 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
edetate disodium	0.4 mg in 1 mL

Product Characteristics

Color	Score
Shape	Size
Flavor	Imprint Code

Contains

Packaging

#	Item Code	Package Description	Multilevel Packaging
1	NDC:0270-0809-75	10 BOTTLE in 1 PACKAGE	contains a BOTTLE
1		300 mL in 1 BOTTLE	This package is contained within the PACKAGE (0270-0809-75)

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA010040	06/24/1970	07/31/2009

Labeler - Bracco Diagnostics Inc (849234661)

Registrant - Bracco Diagnostics Inc (849234661)

Establishment

Name	Address	ID/FEI	Operations
TEVA PHARMACEUTICALS USA		071786802	MANUFACTURE, ANALYSIS

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