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January 17, 2002

Dockets Management Branch  
Food and Drug Administration  
Room 1-23  
12420 Parklawn Dr.  
Rockville, MD 20857

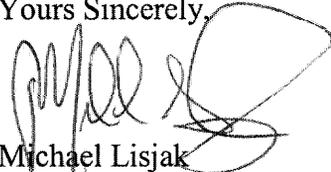
**Citizen Petition**  
**Piperacillin for Injection, USP**

Dear Sir:

Attached are four (4) copies of a Citizen Petition requesting the addition of Pipracil® (40g base/vial), Lederle, to the Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition (the Orange Book). Additionally, since this particular drug product dosage is no longer marketed, this Citizen's Petition seeks the determination whether the listed drug, Pipracil® (40g base/vial), was withdrawn by Lederle for safety or effectiveness reasons.

If you have any questions, please contact the undersigned at (312) 733-9456.

Yours Sincerely,



Michael Lisjak  
934 West Fry Street  
Unit 2W  
Chicago, IL 60622

02P-0043

CP 1

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**CITIZEN PETITION**

The undersigned submits this petition under 21 CFR 10.30 and 314.122 to request the Commissioner of Food and Drugs to grant the Petitioner permission to file an Abbreviated New Drug Application (ANDA) for Piperacillin for Injection, USP (40g base/vial, Pharmacy Bulk Package), which refers to a listed drug which has been voluntarily withdrawn from sale in the United States.

**A. ACTION REQUESTED**

This petition requests the addition of Pipracil<sup>®</sup> (40g base/vial), Lederle, to the Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition (the Orange Book). Additionally, since this particular drug product dosage is no longer marketed, this Citizen's Petition seeks the determination whether the listed drug, Pipracil<sup>®</sup> (40g base/vial), was withdrawn by Lederle for safety or effectiveness reasons.

**B. STATEMENT OF GROUNDS**

The reference product, Pipracil<sup>®</sup> (40g base/vial), is not listed in any part of the Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition (the "Orange Book").

I intend to submit an Abbreviated New Drug Application (ANDA) for Piperacillin for Injection, USP. The proposed drug product will be marketed as Piperacillin for Injection, USP (40g base/vial), which is identical to the previously marketed Lederle product, Pipracil<sup>®</sup> (40g base/vial). A Side-by-Side comparison of the previously marketed drug and the proposed drug is included in the following table.

	<b>Previously Marketed Drug</b>	<b>Proposed Drug</b>
Name	Pipracil <sup>®</sup>	Piperacillin for Injection, USP
Conditions of Use (Indications) <sup>1</sup>	Indicated for the treatment of serious infections caused by susceptible strains of designated organisms in the conditions listed in the package insert. Piperacillin is also indicated for prophylactic use for surgery indicated in the package insert.	Indicated for the treatment of serious infections caused by susceptible strains of designated organisms in the conditions listed in the package insert. Piperacillin is also indicated for prophylactic use for surgery indicated in the package insert.
Active Ingredient	Piperacillin Sodium, USP	Piperacillin Sodium, USP
Dosage Form	Sterile Powder	Sterile Powder
Route of Administration	Intravenous or Intramuscular	Intravenous or Intramuscular
Strength	40g base/vial	40g base /vial

<sup>1</sup> Due to the length of the Indications and Usage section for Piperacillin for Injection, USP, this is only a summary of the indications. For a complete listing of the indications, please refer to Lederle's Package Insert provided in **Attachment 1**.

**C. ENVIRONMENTAL IMPACT**

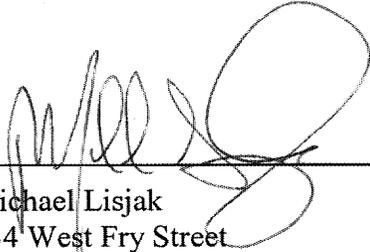
Action on an ANDA is categorically excluded from the requirements of an environmental assessment or impact statement under 21 CFR 25.31 (a).

**D. ECONOMIC IMPACT**

Not Applicable

**E. CERTIFICATION**

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it included representative data and information known to the petitioner, which are unfavorable to the petition.

A handwritten signature in black ink, appearing to read 'Michael Lisjak', is written over a horizontal line. The signature is stylized and somewhat cursive.

Michael Lisjak  
934 West Fry Street  
Unit 2W  
Chicago, IL 60622



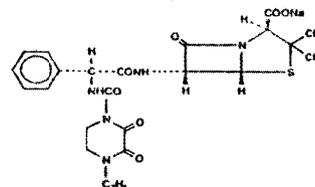
CI 4579-2

# PIPRACIL® (piperacillin sodium)

For Intravenous and Intramuscular Use

**Description**

PIPRACIL (piperacillin sodium) is a semisynthetic broad-spectrum penicillin for parenteral use derived from D(-)- $\alpha$ -aminobenzylpenicillin. The chemical name of piperacillin sodium is 4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 6-[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]phenylacetyl]amino]-3,3-dimethyl-7-oxo-, monosodium salt, [2S-[2 $\alpha$ ,5 $\alpha$ ,6 $\beta$ (S\*)]]. Its structural formula is:



PIPRACIL is a white to off-white solid having the characteristic appearance of products prepared by freeze-drying. Freely soluble in water and in alcohol. The pH of the aqueous solution is 5.5 to 7.5. One g contains 1.85 mEq (42.5 mg) of sodium (Na<sup>+</sup>).

**Clinical Pharmacology**

**Intravenous Administration.** In healthy adult volunteers, mean serum levels immediately after a two to three minute intravenous injection of 2, 4 or 6 g were 305, 412, and 775 mcg/mL. Serum levels lack dose proportionality.

PIPERACILLIN SERUM LEVELS IN ADULTS (mcg/mL) After a two - three minute IV INJECTION												
DOSE	0	10 min	20 min	30 min	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	
2	305 (159-615)	202 (164-225)	155 (52-165)	67 (41-88)	40 (25-57)	24 (18-31)	20 (14-24)	8 (3-11)	3 (2-4)	2 (<0.6-3)	—	
4	412 (389-464)	344 (315-379)	295 (269-330)	117 (98-138)	93 (78-110)	60 (50-67)	36 (26-51)	20 (17-24)	8 (7-11)	4 (3.7-4.1)	0.9 (0.7-1)	
6	775 (695-849)	609 (530-670)	563 (492-630)	325 (292-363)	208 (180-239)	138 (115-175)	90 (71-113)	38 (29-53)	33 (25-44)	8 (3-19)	3.2 (<2-6)	
PIPERACILLIN SERUM LEVELS IN ADULTS (mcg/mL) After a 30-minute IV INFUSION												
DOSE	0	5 min	10 min	15 min	30 min	45 min	1 h	1.5 h	2 h	4 h	6 h	7.5 h
4	244 (155-298)	215 (169-247)	186 (140-209)	177 (142-213)	141 (122-156)	146 (110-265)	105 (85-133)	72 (53-105)	53 (36-69)	15 (6-24)	4 (1-9)	2 (0.5-3)
6	353 (324-371)	298 (242-339)	298 (232-331)	272 (219-314)	229 (185-249)	180 (144-209)	149 (117-171)	104 (89-113)	73 (66-94)	22 (12-39)	16 (5-49)	—

A 30-minute infusion of 6 g every 6 h gave, on the fourth day, a mean peak serum concentration of 420 mcg/mL.

**Intramuscular Administration.** PIPRACIL is rapidly absorbed after intramuscular injection. In healthy volunteers, the mean peak serum concentration occurs approximately 30 minutes after a single dose of 2 g and is about 36 mcg/mL. The oral administration of 1 g probenecid before injection produces an increase in piperacillin peak serum level of about 30%. The area under the curve (AUC) is increased by approximately 60%.

**GENERAL**

PIPRACIL is not absorbed when given orally. Peak serum concentrations are attained approximately 30 minutes after intramuscular injections and immediately after completion of intravenous injection or infusion. The serum half-life in healthy volunteers ranges from 36 minutes to one hour and 12 minutes. The mean elimination half-life of PIPRACIL in healthy adult volunteers is 54 minutes following administration of 2 g and 63 minutes following 6 g. As with other penicillins, PIPRACIL is eliminated primarily by glomerular filtration and tubular secretion; it is excreted rapidly as unchanged drug in high concentrations in the urine. Approximately 60% to 80% of the administered dose is excreted in the urine in the first 24 hours. Piperacillin urine concentrations, determined by microbioassay, were as high as 14,100 mcg/mL following a 6 g intravenous dose and 8,500 mcg/mL following a 4 g intravenous dose. These urine drug concentrations remained well above 1,000 mcg/mL throughout the dosing interval. The elimination half-life is increased twofold in mild to moderate renal impairment and fivefold to sixfold in severe impairment.

PIPRACIL binding to human serum proteins is 16%. The drug is widely distributed in human tissues and body fluids, including bone, prostate, and heart and reaches high concentrations in bile. After a 4 g bolus, maximum biliary concentrations averaged 3,205 mcg/mL. It penetrates into the cerebrospinal fluid in the presence of inflamed meninges. Because PIPRACIL is excreted by the biliary route as well as by the renal route, it can be used safely in appropriate dosage (see **Dosage and Administration**) in patients with severely restricted kidney function, and can be used effectively in treatment of hepatobiliary infections.

**MICROBIOLOGY**

PIPRACIL is an antibiotic which exerts its bactericidal activity by inhibiting both septum and cell wall synthesis. It is active against a variety of gram-positive and gram-negative aerobic and anaerobic bacteria. *In vitro*, piperacillin is active against most strains of clinical isolates of the following microorganisms:

*Aerobic and facultatively anaerobic organisms*  
Gram-negative bacteria  
*Escherichia coli*

against anaerobes and enterococci.

*In vitro* tests show piperacillin to act synergistically with aminoglycoside antibiotics against most isolates of *P. aeruginosa*.

**SUSCEPTIBILITY TESTING**

The use of a 100 mcg piperacillin antibiotic disk with susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of organisms to PIPRACIL. The following standard procedure<sup>1</sup> has been recommended for use with disks for testing antimicrobials.

<sup>1</sup>NCCLS Approved Standard; M2-A2 (Formerly ASM-2) Performance Standards for Antimicrobial Disk Susceptibility Tests, Second Edition, available from the National Committee of Clinical Laboratory Standards.

With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (eg, urine) in which high antibiotic levels are obtained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With the piperacillin disk, a zone of 18 mm or greater indicates susceptibility, zone sizes of 14 mm or less indicate resistance, and zone sizes of 15 to 17 mm indicate intermediate susceptibility.

*Haemophilus* and *Neisseria* species which give zones of  $\geq 29$  mm are susceptible; resistant strains give zones of  $\leq 28$  mm. The above interpretive criteria are based on the use of the standardized procedure. Antibiotic susceptibility testing requires carefully prescribed procedures. Susceptibility tests are biased to a considerable degree when different methods are used.

The standardized procedure requires the use of control organisms. The 100 mcg piperacillin disk should give zone diameters between 24 and 30 mm for *E. coli* ATCC No. 25922 and between 25 and 33 mm for *Pseudomonas aeruginosa* ATCC No. 27853.

Dilution methods such as those described in the International Collaborative study<sup>2</sup> have been used to determine susceptibility of organisms to PIPRACIL.

<sup>2</sup>*Acta Pathol Microbiol Scand* [8] 1971; suppl 217.

*Enterobacteriaceae*, *Pseudomonas* species and *Acinetobacter* sp are considered susceptible if the minimal inhibitory concentration (MIC) of piperacillin is no greater than 64 mcg/mL and are considered resistant if the MIC is greater than 128 mcg/mL.

*Haemophilus* and *Neisseria* species are considered susceptible if the MIC of piperacillin is  $\leq 1$  mcg/mL.

*Proteus mirabilis*  
*Proteus vulgaris*  
*Morganella morganii* (formerly *Proteus morganii*)  
*Providencia rettgeri* (formerly *Proteus rettgeri*)  
*Serratia* species including *S. marcescens* and *S. liquefaciens*  
*Klebsiella pneumoniae*  
*Klebsiella* species  
*Enterobacter* species including *E. aerogenes* and *E. cloacae*  
*Citrobacter* species including *C. freundii* and *C. diversus*  
*Salmonella* species\*  
*Shigella* species\*  
*Pseudomonas aeruginosa*  
*Pseudomonas* species including *P. cepacia*, \* *P. maltophilia*, \* *P. fluorescens*  
*Acinetobacter* species (formerly *Mima-Herellea*)  
*Haemophilus influenzae* (non- $\beta$ -lactamase-producing strains)  
*Neisseria gonorrhoeae*  
*Neisseria meningitidis*\*  
*Moraxella* species\*  
*Yersinia* species\* (formerly *Pasteurella*)  
**Gram-positive bacteria**  
 Group D streptococci including  
   Enterococci (*Streptococcus faecalis*, *S. faecium*)  
   Non-enterococci\*  
 $\beta$ -hemolytic streptococci including  
   Group A *Streptococcus* (*S. pyogenes*)  
   Group B *Streptococcus* (*S. agalactiae*)  
*Streptococcus pneumoniae*  
*Streptococcus viridans*  
*Staphylococcus aureus* (non-penicillinase-producing)\*  
*Staphylococcus epidermidis* (non-penicillinase-producing)\*  
**Aerobic bacteria**  
*Actinomyces* species\*  
*Bacteroides* species including  
   *B. fragilis* group (*B. fragilis*, *B. vulgatus*)  
   Non-*B. fragilis* group (*B. melaninogenicus*)  
   *B. asaccharolyticus*\*  
*Clostridium* species including *C. perfringens* and *C. difficile*\*  
*Eubacterium* species  
*Fusobacterium* species including *F. nucleatum* and *F. necrophorum*  
*Peptococcus* species  
*Peptostreptococcus* species  
*Veillonella* species

\*Piperacillin has been shown to be active *in vitro* against these organisms; however, clinical efficacy has not yet been established.

*In vitro*, PIPRACIL is inactivated by staphylococcal  $\beta$ -lactamases and  $\beta$ -lactamases produced by gram-negative bacteria. However, it is active against  $\beta$ -lactamase-producing gonococci. Many strains of gram-negative organisms resistant to certain antibiotics have been found to be susceptible to PIPRACIL.

PIPACIL has excellent activity against gram-positive organisms, including enterococci (*S. faecalis*). It is active against obligate anaerobes such as *Bacteroides* species and also against *C. difficile* (which has been associated with pseudomembranous colitis). Piperacillin is active against many gram-negative bacteria including *Enterobacteriaceae*, *Klebsiella*, *Serratia*, *Pseudomonas*, *E. coli*, *Proteus*, and *Citrobacter*, and, in addition, it is active

When anaerobic organisms are isolated from infection sites, it is recommended that other tests such as the modified Broth-Disk Method<sup>5</sup> be used to determine the antibiotic susceptibility of these slowly growing organisms.

Swilkins TD and Thiel T: *Antimicrob Agents Chemother* 1973; 3:350-356.

#### Indications and Usage

**Therapeutic.** PIPRACIL is indicated for the treatment of serious infections caused by susceptible strains of the designated organisms in the conditions as listed below.

**Intra-Abdominal Infections** including hepatobiliary and surgical infections caused by *E. coli*, *P. aeruginosa*, enterococci, *Clostridium* sp, anaerobic cocci, and *Bacteroides* sp, including *B. fragilis*.

**Urinary Tract Infections** caused by *E. coli*, *Klebsiella* sp, *P. aeruginosa*, *Proteus* sp, including *P. mirabilis*, and enterococci.

**Gynecologic Infections** including endometritis, pelvic inflammatory disease, pelvic cellulitis caused by *Bacteroides* sp including *B. fragilis*, anaerobic cocci, *Neisseria gonorrhoeae*, and enterococci (*S. faecalis*).

**Septicemia**, including bacteremia caused by *E. coli*, *Klebsiella* sp, *Enterobacter* sp, *Serratia* sp, *P. mirabilis*, *S. pneumoniae*, enterococci, *P. aeruginosa*, *Bacteroides* sp and anaerobic cocci.

**Lower Respiratory Tract Infections** caused by *E. coli*, *Klebsiella* sp, *Enterobacter* sp, *Pseudomonas aeruginosa*, *Serratia* sp, *H. influenzae*, *Bacteroides* sp, and anaerobic cocci.

Although improvement has been noted in patients with cystic fibrosis, lasting bacterial eradication may not necessarily be achieved.

**Skin and Skin Structure Infections** caused by *E. coli*, *Klebsiella* sp, *Serratia* sp, *Acinetobacter* sp, *Enterobacter* sp, *Pseudomonas aeruginosa*, indole-positive *Proteus* sp, *Proteus mirabilis*, *Bacteroides* sp, including *B. fragilis*, anaerobic cocci, and enterococci.

**Bone and Joint Infections** caused by *P. aeruginosa*, enterococci, *Bacteroides* sp, and anaerobic cocci.

**Gonococcal Infections.** PIPRACIL has been effective in the treatment of uncomplicated gonococcal urethritis.

PIPACIL has also been shown to be clinically effective for the treatment of infections at various sites caused by *Streptococcus* species including Group A  $\beta$ -hemolytic *Streptococcus* and *S. pneumoniae*; however, infections caused by these organisms are ordinarily treated with more narrow spectrum penicillins. Because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic bacteria, PIPRACIL is particularly useful for the treatment of mixed infections and presumptive therapy prior to the identification of the causative organisms.

Also, PIPRACIL may be administered as single drug therapy in some situations where normally two antibiotics might be employed.

Piperacillin has been successfully used with aminoglycosides, especially in patients with impaired host defenses. Both drugs should be used in full therapeutic doses.

Appropriate cultures should be made for susceptibility testing before initiating therapy and therapy adjusted, if appropriate, once the results are known.

**Prophylaxis.** PIPRACIL is indicated for prophylactic use in surgery including intra-abdominal (gastrointestinal and biliary) procedures, vaginal hysterectomy, abdominal hysterectomy, and cesarean section. Effective prophylactic use depends on the time of administration and PIPRACIL should be given one-half to one hour before the operation so that effective levels can be achieved in the site prior to the procedure.

The prophylactic use of piperacillin should be stopped within 24 hours, since continuing administration of any antibiotic increases the possibility of adverse reactions, but in the majority of surgical procedures, does not reduce the incidence of subsequent infections. If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy can be instituted.

#### Contraindications

A history of allergic reactions to any of the penicillins and/or cephalosporins.

#### Warnings

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of sensitivity to multiple allergens.

There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with PIPRACIL, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs during therapy with PIPRACIL, the antibiotic should be discontinued. The usual agents (antihistamines, pressor amines, and corticosteroids) should be readily available. SERIOUS

ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN AND INTRAVENOUS CORTICOSTEROIDS AND AIRWAY MANAGEMENT INCLUDING INTUBATION SHOULD ALSO BE ADMINISTERED AS NECESSARY.

#### Precautions

##### GENERAL

While piperacillin possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions including renal, hepatic, and hematopoietic during prolonged therapy is advisable.

Bleeding manifestations have occurred in some patients receiving  $\beta$ -lactam antibiotics, including piperacillin. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal failure.

If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.

The possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

PIPRACIL is a monosodium salt containing 1.85 mEq of  $\text{Na}^+$  per g. This should be considered when treating patients requiring restricted salt intake. Periodic electrolyte determinations should be made in patients with low potassium reserves, and the possibility of hypokalemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving cytotoxic therapy or diuretics.

Antimicrobials used in high doses for short periods to treat gonorrhea may mask or delay the symptoms of incubating syphilis. Therefore, prior to treatment, patients with gonorrhea should also be evaluated for syphilis. Specimens for darkfield examination should be obtained from patients with any suspected primary lesion, and serologic tests should be performed. In all cases where concomitant syphilis is suspected, monthly serological tests should be made for a minimum of 4 months.

As with other semisynthetic penicillins, PIPRACIL therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

##### Drug Interactions

The mixing of piperacillin with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycosides.

Piperacillin when used concomitantly with vecuronium has been implicated in the prolongation of the neuromuscular blockage of vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarizing muscle relaxants could be prolonged in the presence of piperacillin. (See package insert for vecuronium bromide.)

##### Pregnancy - Pregnancy Category B

Although reproduction studies in mice and rats performed at doses up to 4 times the human dose have shown no evidence of impaired fertility or harm to the fetus, safety of PIPRACIL use in pregnant women has not been determined by adequate and well-controlled studies. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. It has been found to cross the placenta in rats.

##### Nursing Mothers

Caution should be exercised when PIPRACIL is administered to nursing mothers. It is excreted in low concentrations in milk.

##### Pediatric Use

Dosages for children under the age of 12 have not been established. The safety of PIPRACIL in neonates is not known. In dog neonates dilated renal tubules and peritubular hyalinization occurred following administration of PIPRACIL.

##### Adverse Effects

PIPRACIL is generally well tolerated. The most common adverse reactions have been local in nature, following intravenous or intramuscular injection. The following adverse reactions may occur.

**Local Reactions.** In clinical trials thrombophlebitis was noted in 4% of patients. Pain, erythema, and/or induration at the injection site occurred in 2% of patients. Less frequent reactions including ecchymosis, deep vein thrombosis and hematomas have also occurred.

**Gastrointestinal.** Diarrhea and loose stools were noted in 2% of patients. Other less frequent reactions included vomiting, nausea, increases in liver enzymes. (LDH, SGOT, SGPT), hyperbilirubinemia, cholestatic hepatitis, bloody diarrhea and, rarely, pseudomembranous colitis.

**Hypersensitivity Reactions.** Anaphylactoid Reactions, see Warnings

##### Prophylaxis

When possible, PIPRACIL should be administered as a 20-30 minute infusion just prior to anaesthesia. Administration while the patient is awake will facilitate identification of possible adverse reactions during drug infusion.

INDICATION	1st Dose	2nd Dose	3rd Dose
Intra-abdominal Surgery	2 g IV just prior to surgery	2 g during surgery	2 g every 6 h Post-Op for no more than 24 h
Vaginal Hysterectomy	2 g IV just prior to surgery	2 g 6 h after 1st dose	2 g 12 h after 1st dose
Cesarean Section	2 g IV after cord is clamped	2 g 4 h after 1st dose	2 g 8 h after 1st dose
Abdominal Hysterectomy	2 g IV just prior to surgery	2 g on return to recovery room	2 g after 6 h

*Infants and Children.* Dosages in infants and children under 12 years of age have not been established.

#### PRODUCT RECONSTITUTION/DOSAGE PREPARATION

##### Conventional Vials:

Sterile Water for Injection  
Bacteriostatic Water for Injection  
†Either Parabens or Benzyl Alcohol

##### Diluents for Reconstitution

Sodium Chloride Injection  
Bacteriostatic Sodium Chloride Injection  
Dextrose 5% in Water  
Dextrose 5% and 0.9% Sodium Chloride  
‡Lidocaine HCl 0.5-1% (without epinephrine)

‡For Intramuscular Use Only. Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.

##### Conventional Vials:

###### Intravenous Solutions

Dextrose 5% in Water  
0.9% Sodium Chloride  
Dextrose 5% and 0.9% Sodium Chloride  
Lactated Ringer's Injection††  
Dextran 6% in 0.9% Sodium Chloride

###### Intravenous Admixtures

Normal Saline [+ KCl 40 mEq]  
5% Dextrose in Water [+ KCl 40 mEq]  
5% Dextrose/Normal Saline [+ KCl 40 mEq]  
Ringer's Injection [+ KCl 40 mEq]  
Lactated Ringer's Injection [+ KCl 40 mEq]††

††When PIPRACIL\* is further diluted with Lactated Ringer's Injection, the diluted solution must be administered within 2 hours.

##### ADD-Vantage\*\* Vials:

###### ADD-Vantage System Admixtures

Dextrose 5% in Water (50 or 100 mL)  
0.9% Sodium Chloride (50 or 100 mL)

\*\* (ADD-Vantage is the registered trademark of Abbott Laboratories)

##### Intravenous Administration

**Reconstitution Directions for Conventional Vials:** Reconstitute each gram of PIPRACIL with at least 5 mL of a suitable diluent (except Lidocaine HCl 0.5%-1% without epinephrine) listed above. Shake well until dissolved. Reconstituted solution may be further diluted to the desired volume (eg, 50 or 100 mL) in the above listed intravenous solutions and admixtures.

**Reconstitution Directions for ADD-Vantage Vials:** See Instruction Sheet provided in box.

**Reconstitution Directions for PHARMACY BULK VIAL:** Reconstitute the 40 g vial with 172 mL of a suitable diluent (except Lidocaine HCl 0.5%-1% without epinephrine) listed above to achieve a concentration of 1 g per 5 mL.

##### DIRECTIONS FOR ADMINISTRATION

###### Intermittent IV Infusion

Infuse diluted solution over period of about 30 minutes. During infusion it is desirable to dis-

Rash was noted in 1% of patients. Other less frequent findings included pruritus, vesicular eruptions, positive Coombs tests.

Other dermatologic manifestations, such as erythema multiforme and Stevens-Johnson syndrome have been reported rarely.

**Renal:** Elevations of creatinine or BUN, and rarely, interstitial nephritis.

**Central Nervous System:** Headache, dizziness, fatigue.

**Hemic and Lymphatic:** Reversible leukopenia, neutropenia, thrombocytopenia and/or eosinophilia have been reported. As with other  $\beta$ -lactam antibiotics, reversible leukopenia (neutropenia) is more apt to occur in patients receiving prolonged therapy at high dosages or in association with drugs known to cause this reaction.

**Serum Electrolytes:** Individuals with liver disease or individuals receiving cytotoxic therapy or diuretics were reported rarely to demonstrate a decrease in serum potassium concentrations with high doses of piperacillin.

**Skeletal:** Rarely, prolonged muscle relaxation.

**Other:** Superinfection, including candidiasis. Hemorrhagic manifestations.

#### Dosage and Administration

PIPRACIL may be administered by the intramuscular route (see NOTE) or intravenously or given in a three to five minute intravenous injection. The usual dosage of PIPRACIL for serious infections is 3- to 4-g given every four to six hours as a 20- to 30-minute infusion. For serious infections, the intravenous route should be used.

PIPRACIL should not be mixed with an aminoglycoside in a syringe or infusion bottle since this can result in inactivation of the aminoglycoside.

The maximum daily dose for adults is usually 24 g/day, although higher doses have been used. Intramuscular injections (See NOTE) should be limited to 2 g per injection site. This route of administration has been used primarily in the treatment of patients with uncomplicated gonorrhea and urinary tract infections.

NOTE: THE ADD-VANTAGE VIAL IS NOT FOR IM USE

#### DOSAGE RECOMMENDATIONS

Type of Infection	Usual Total Daily Dose
Serious infections such as septicemia, nosocomial pneumonia, intra-abdominal infections, aerobic and anaerobic gynecologic infections, and skin and soft tissue infections	12 - 18 g/d IV (200 - 300 mg/kg/d) in divided doses every 4 to 6 h
Complicated urinary tract infections	8 - 16 g/d IV (125 - 200 mg/kg/d) in divided doses every 6 to 8 h
Uncomplicated urinary tract infections and most community-acquired pneumonia	6 - 8 g/d IM or IV (100 - 125 mg/kg/d) in divided doses every 6 to 12 h
Uncomplicated gonorrhea infections	2 g IM <sup>II</sup> as a one-time dose

One g of probenecid given orally one-half hour prior to injection.

The average duration of PIPRACIL treatment is from seven to ten days, except in the treatment of gynecologic infections, in which it is from three to ten days, the duration should be guided by the patient's clinical and bacteriological progress. For most acute infections, treatment should be continued for at least 48 to 72 hours after the patient becomes asymptomatic. Antibiotic therapy for Group A  $\beta$ -hemolytic streptococcal infections should be maintained for at least ten days to reduce the risk of rheumatic fever or glomerulonephritis.

When PIPRACIL is given concurrently with aminoglycosides, both drugs should be used in full therapeutic doses.

#### Renal Impairment

##### Dosage in Renal Impairment

Creatinine Clearance mL/min	Urinary Tract Infection (uncomplicated)	Urinary Tract Infection (complicated)	Serious Systemic Infection
>40	No dosage adjustment necessary		
20-40	No dosage adjustment necessary	9 g/day 3 g every 8 h	12 g/day 4 g every 8 h
<20	6 g/day 3 g every 12 h	6 g/day 3 g every 12 h	8 g/day 4 g every 12 h

For patients on hemodialysis the maximum daily dose is 6 g/day (2 g every 8 hours). In addition, because hemodialysis removes 30%-50% of piperacillin in 4 hours, 1 g additional dose should be administered following each dialysis period.

For patients with renal failure and hepatic insufficiency measurement of serum levels of PIPRACIL will provide additional guidance for adjusting dosage.

continue the primary intravenous solution.

#### Intravenous Injection (Bolus)

Reconstituted solution should be injected slowly over a 3- to 5-minute period to help avoid vein irritation.

#### Intramuscular Administration (Conventional Vials Only)

**Reconstitution Directions:** Reconstitute each gram of PIPRACIL with 2 mL of a suitable diluent listed above to achieve a concentration of 1 g per 2.5 mL. Shake well until dissolved.

#### DIRECTIONS FOR ADMINISTRATION

When indicated by clinical and bacteriological findings, intramuscular administration of 6 to 8 g daily of PIPRACIL, in divided doses, may be utilized for initiation of therapy. In addition, intramuscular administration of the drug may be considered for maintenance therapy after clinical and bacteriologic improvement has been obtained with intravenous piperacillin sodium treatment. Intramuscular administration should not exceed 2 g per injection at any one site.

The preferred site is the upper outer quadrant of the buttock (ie, *gluteus maximus*).

The deltoid area should be used only if well-developed, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower or mid-third of the upper arm.

#### Stability of PIPRACIL Following Reconstitution

PIPRACIL is stable in both glass and plastic containers when reconstituted with recommended diluents and when diluted with the intravenous solutions and intravenous admixtures indicated above.

Extensive stability studies have demonstrated chemical stability (potency, pH, and clarity) through 24 hours at room temperature, up to one week refrigerated, and up to one month frozen (-10° to -20°C). (Note: The 40 g Pharmacy Bulk Vial should not be frozen after reconstitution.) Appropriate consideration of aseptic technique and individual hospital policy, however, may recommend discarding unused portions after storage for 48 hours under refrigeration and discarding after 24 hours storage at room temperature.

#### ADD-VANTAGE SYSTEM

Stability studies with the ad-mixed ADD-Vantage system have demonstrated chemical stability (potency, pH and clarity) through 24 hours at room temperature. (Note: The ad-mixed ADD-Vantage should not be refrigerated or frozen after reconstitution.)

Additional stability data available upon request.

#### How Supplied

PIPRACIL (piperacillin sodium) is available in vials containing freeze-dried piperacillin sodium powder equivalent to two, three, four and 40 g of piperacillin. One g of piperacillin (as a monosodium salt) contains 1.85 mEq (42.5 mg) of sodium.

#### Product Numbers

2 gram/Vial - 10 per box - NDC 0206-3879-16
3 gram/Vial - 10 per box - NDC 0206-3882-55
4 gram/Vial - 10 per box - NDC 0206-3880-25
3 gram infusion Bottle - 10 per box - NDC 0206-3882-65
4 gram infusion Bottle - 10 per box - NDC 0206-3880-66
2 gram ADD-Vantage Vial - 10 per box - NDC 0206-3879-27
3 gram ADD-Vantage Vial - 10 per box - NDC 0206-3882-28
4 gram ADD-Vantage Vial - 10 per box - NDC 0206-3880-29
40 gram Pharmacy Bulk Vial - NDC 0206-3677-60

Store at controlled room temperature 15-30°C (59-86°F).

Caution: Federal law prohibits dispensing without prescription.



LEDERLE  
PIPERACILLIN, INC.  
Carolina, Puerto Rico 00987



January 17, 2002

Dockets Management Branch  
Food and Drug Administration  
Room 1-23  
12420 Parklawn Dr.  
Rockville, MD 20857

**Citizen Petition**  
**Piperacillin for Injection, USP**

Dear Sir:

Attached are four (4) copies of a Citizen Petition requesting the addition of Pipracil® (40g base/vial), Lederle, to the Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition (the Orange Book). Additionally, since this particular drug product dosage is no longer marketed, this Citizen's Petition seeks the determination whether the listed drug, Pipracil® (40g base/vial), was withdrawn by Lederle for safety or effectiveness reasons.

If you have any questions, please contact the undersigned at (312) 733-9456.

Yours Sincerely,



Michael Lisjak  
934 West Fry Street  
Unit 2W  
Chicago, IL 60622

## CITIZEN PETITION

The undersigned submits this petition under 21 CFR 10.30 and 314.122 to request the Commissioner of Food and Drugs to grant the Petitioner permission to file an Abbreviated New Drug Application (ANDA) for Piperacillin for Injection, USP (40g base/vial, Pharmacy Bulk Package), which refers to a listed drug which has been voluntarily withdrawn from sale in the United States.

### A. ACTION REQUESTED

This petition requests the addition of Pipracil<sup>®</sup> (40g base/vial), Lederle, to the Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition (the Orange Book). Additionally, since this particular drug product dosage is no longer marketed, this Citizen's Petition seeks the determination whether the listed drug, Pipracil<sup>®</sup> (40g base/vial), was withdrawn by Lederle for safety or effectiveness reasons.

### B. STATEMENT OF GROUNDS

The reference product, Pipracil<sup>®</sup> (40g base/vial), is not listed in any part of the Approved Drug Products with Therapeutic Equivalence Evaluations, 20<sup>th</sup> Edition (the "Orange Book").

I intend to submit an Abbreviated New Drug Application (ANDA) for Piperacillin for Injection, USP. The proposed drug product will be marketed as Piperacillin for Injection, USP (40g base/vial), which is identical to the previously marketed Lederle product, Pipracil<sup>®</sup> (40g base/vial). A Side-by-Side comparison of the previously marketed drug and the proposed drug is included in the following table.

	Previously Marketed Drug	Proposed Drug
Name	Pipracil <sup>®</sup>	Piperacillin for Injection, USP
Conditions of Use (Indications) <sup>1</sup>	Indicated for the treatment of serious infections caused by susceptible strains of designated organisms in the conditions listed in the package insert. Piperacillin is also indicated for prophylactic use for surgery indicated in the package insert.	Indicated for the treatment of serious infections caused by susceptible strains of designated organisms in the conditions listed in the package insert. Piperacillin is also indicated for prophylactic use for surgery indicated in the package insert.
Active Ingredient	Piperacillin Sodium, USP	Piperacillin Sodium, USP
Dosage Form	Sterile Powder	Sterile Powder
Route of Administration	Intravenous or Intramuscular	Intravenous or Intramuscular
Strength	40g base/vial	40g base /vial

<sup>1</sup> Due to the length of the Indications and Usage section for Piperacillin for Injection, USP, this is only a summary of the indications. For a complete listing of the indications, please refer to Lederle's Package Insert provided in **Attachment 1**.

**C. ENVIRONMENTAL IMPACT**

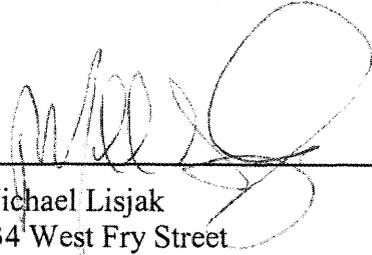
Action on an ANDA is categorically excluded from the requirements of an environmental assessment or impact statement under 21 CFR 25.31 (a).

**D. ECONOMIC IMPACT**

Not Applicable

**E. CERTIFICATION**

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it included representative data and information known to the petitioner, which are unfavorable to the petition.



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Michael Lisjak  
934 West Fry Street  
Unit 2W  
Chicago, IL 60622