

088239
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PIVVA safely and effectively. See full prescribing information for PIVVA (pivmecillinam) tablets, for oral use.

Initial U.S. Approval: 2024
INDICATIONS AND USAGE
PIVVA is a penicillin class antibacterial indicated for the treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (UTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus saprophyticus*. (1.1)
To reduce the development of drug-resistant bacteria and maintain the effectiveness of PIVVA and other antibacterial drugs, PIVVA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)
DOSE AND ADMINISTRATION
• The recommended dosage of PIVVA is one 185 mg tablet orally 3 times a day for 7 to 10 days as clinically indicated. (2.1)
• Administer PIVVA with or without food. (2.1)
DOSE FORMS AND STRENGTHS
Tablets: 185 mg pivmecillinam.
CONTRAINDICATIONS
• Serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to PIVVA or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins). (4.1)
• Primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, and other inborn errors of metabolism (e.g., methylmalonic aciduria, or propionic acidemia). (4.2)
• Acute porphyria. (4.3)

WARNINGS AND PRECAUTIONS
• Hypersensitivity Reactions: Serious hypersensitivity reactions including anaphylaxis have been reported in patients treated with PIVVA. If hypersensitivity reactions occur, discontinue treatment with PIVVA and institute appropriate therapy. (5.1)
• Severe Cutaneous Adverse Reactions (SCAR): Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with PIVVA. Monitor patients closely and discontinue PIVVA at the first signs or symptoms of SCAR or other signs of hypersensitivity. (5.2)
• Carnitine Depletion: Clinically significant hypocarnitemia has been observed in patients at risk for reductions in serum carnitine. In patients with significant carnitine impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment, consider alternative antimicrobial therapies. PIVVA is not recommended when prolonged antimicrobial treatment is necessary. Avoid concurrent treatment with valproic acid, valproate or other pivalate-generating drugs due to increased risk of carnitine depletion. (5.3)
• Clostridioides difficile-Associated Diarrhea (CDAD): This has been reported for nearly all systemic antibacterial agents, including PIVVA. Evaluate diarrhea that occurs (5.4)
• Interference with Newborn Screening Test: Treatment of a pregnant individual with PIVVA prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening. Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended. (5.7)
ADVERSE REACTIONS
The most common adverse reactions observed in 22% of the patients receiving PIVVA in clinical trials are nausea and diarrhea (6.1).

To report suspected adverse reactions, contact Allergan Therapeutics at 1-866-210-9797 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION
Revised: 2/2025

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FULL PRESCRIBING INFORMATION:
INDICATIONS AND USAGE
1.1 Uncomplicated Urinary Tract Infections
PIVVA is indicated for the treatment of female patients 18 years of age and older with uncomplicated urinary tract infections (uUTI) caused by susceptible isolates of *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus saprophyticus*. (1.1)
1.2 Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of PIVVA and other antibacterial drugs, PIVVA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Do not double the dose to make up for the missed dose.
2 DOSE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage of PIVVA is one 185 mg tablet orally 3 times a day for 7 to 10 days as clinically indicated. Administer PIVVA with or without food [see *Clinical Pharmacology* (12.3)].

PIVVA (pivmecillinam) is a prodrug of meccillinam (the active antibacterial agent) [see *Clinical Pharmacology* (12.3)].
2.2 Recommendations Regarding Missed Doses)
If a dose of PIVVA is missed, instruct patients to take the dose as soon as possible. Do not double the dose to make up for the missed dose.
3 DOSE FORMS AND STRENGTHS
Each film-coated tablet contains 185 mg pivmecillinam (equivalent to 200 mg pivmecillinam). The tablet is a white, circular film-coated tablet with a diameter of 9.5 mm, debossed with "P" on one side and blank on the other.
4 CONTRAINDICATIONS
4.1 Serious Hypersensitivity Reactions
PIVVA is contraindicated in patients who have experienced a serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to PIVVA or other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins) [see *Warnings and Precautions* (5.1)].
4.2 Carnitine Deficiency
PIVVA is contraindicated in patients with primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, and other inborn errors of metabolism (e.g., methylmalonic aciduria, or propionic acidemia) [see *Warnings and Precautions* (5.3)].
4.3 Acute Porphyria
PIVVA is contraindicated in patients suffering from porphyria [see *Warnings and Precautions* (5.4)].

5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity Reactions
Serious hypersensitivity reactions (anaphylaxis) have been reported in patients treated with PIVVA [see *Adverse Reactions* (6.1)]. These reactions are more likely to occur in individuals with a history of penicillin, cephalosporin, or streptomycin hypersensitivity or a history of sensitivity to multiple allergens. Before initiating therapy with PIVVA, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and streptomycin, and other beta-lactams because cross-hypersensitivity has been reported. PIVVA is contraindicated in patients who have experienced a serious hypersensitivity reaction [see *Contraindications* (4.1)]. If an allergic reaction occurs, discontinue PIVVA and institute appropriate therapy.
5.2 Severe Cutaneous Adverse Reactions
Severe Cutaneous Adverse Reactions (SCAR) including Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with PIVVA [see *Adverse Reactions* (6.2)]. Monitor patients closely and discontinue PIVVA at the first signs or symptoms of SCAR or other signs of hypersensitivity.
5.3 Carnitine Depletion
Clinical manifestations of carnitine depletion may occur with pivalate-containing compounds, including PIVVA. Symptoms of carnitine depletion include hypoglycemia, hypokalemia, fatigue, and confusion. PIVVA is contraindicated in patients with primary or secondary carnitine deficiency resulting from inherited metabolic disorders known to cause carnitine depletion [see *Contraindications* (4.2)].
No clinical effects of decreased carnitine have been associated with short-term treatment of PIVVA. Clinically significant hypocarnitemia has been observed in patients receiving long term treatment with pivmecillinam. PIVVA is not recommended when prolonged antimicrobial treatment is necessary. The effects on carnitine concentrations of repeated short-term courses of PIVVA are not known. In a study of patients with reductions in serum carnitine (e.g., patients with significant renal impairment or decreased muscle mass) receiving PIVVA, carnitine levels were restored. Avoid concurrent treatment with valproic acid, valproate or other pivalate-generating drugs due to the increased risk of carnitine depletion [see *Drug Interactions* (7.1)].
5.4 Acute Porphyria
PIVVA is contraindicated in patients suffering from porphyria as pivmecillinam has been associated with acute attacks of porphyria [see *Contraindications* (4.3)].

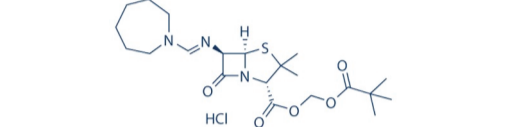
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety of PIVVA was evaluated in 579 adult female patients with uUTI who received PIVVA at a dose of 185 mg three times daily, or at higher daily doses (not approved for PIVVA) for 7 to 10 days in a placebo-controlled trial (Trial 1, N=282), an active-controlled trial (Trial 2, N=213) and an open-label trial (Trial 3, N=84). The majority of patients were White women between 18 and 61 years of age.
No serious adverse reactions were reported in patients treated with PIVVA in the trials.

with PIVVA. If hypersensitivity reactions occur, discontinue treatment with PIVVA and institute appropriate therapy. (5.1)
• Severe Cutaneous Adverse Reactions (SCAR): Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with PIVVA. Monitor patients closely and discontinue PIVVA at the first signs or symptoms of SCAR or other signs of hypersensitivity. (5.2)
• Carnitine Depletion: Clinically significant hypocarnitemia has been observed in patients at risk for reductions in serum carnitine. In patients with significant carnitine impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment, consider alternative antimicrobial therapies. PIVVA is not recommended when prolonged antimicrobial treatment is necessary. Avoid concurrent treatment with valproic acid, valproate or other pivalate-generating drugs due to increased risk of carnitine depletion. (5.3)
• Clostridioides difficile-Associated Diarrhea (CDAD): This has been reported for nearly all systemic antibacterial agents, including PIVVA. Evaluate diarrhea that occurs (5.4)
• Interference with Newborn Screening Test: Treatment of a pregnant individual with PIVVA prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening. Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended. (5.7)
ADVERSE REACTIONS
The following clinically significant adverse reactions are described in greater detail in the Warnings and Precautions section of labeling:
• Hypersensitivity Reactions [see *Warnings and Precautions* (5.1)]
• Severe Cutaneous Adverse Reactions [see *Warnings and Precautions* (5.2)]
• Carnitine Depletion [see *Warnings and Precautions* (5.3)]
• Acute Porphyria [see *Warnings and Precautions* (5.4)]
• Clostridioides difficile-Associated Diarrhea [see *Warnings and Precautions* (5.5)]
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The safety of PIVVA was evaluated in 579 adult female patients with uUTI who received PIVVA at a dose of 185 mg three times daily, or at higher daily doses (not approved for PIVVA) for 7 to 10 days in a placebo-controlled trial (Trial 1, N=282), an active-controlled trial (Trial 2, N=213) and an open-label trial (Trial 3, N=84). The majority of patients were White women between 18 and 61 years of age.
No serious adverse reactions were reported in patients treated with PIVVA in the trials.

on the effects of meccillinam on milk production.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PIVVA and any potential adverse effects on the breastfed child from PIVVA, from the underlying maternal condition.
Data from a study of lactating cows given 8 mg/kg meccillinam IV, the concentration in milk was 0.1 and 0.7 µg/mL at 2 and 6 hours, respectively, and the total excretion in milk over the first 6 hours was 0.03% of the injected dose. The concentration of meccillinam in animal milk does not necessarily predict the concentration of drug in human milk.
8.4 Pediatric Use
The safety and effectiveness of PIVVA have not been established in pediatric patients.
Carnitine Depletion
Symptomatic hypocarnitemia has been reported in pediatric patients outside the United States on long term pivmecillinam therapy. In these cases, irritability, altered mental status, fatigue, muscle weakness, and vomiting have occurred. PIVVA is not recommended when prolonged antimicrobial treatment is necessary [see *Warnings and Precautions* (5.3)]. PIVVA is contraindicated in patients with primary or secondary carnitine deficiency [see *Contraindications* (4.2)].
Interference with Newborn Screening Test
Newborns exposed to PIVVA in utero prior to delivery may have a false positive newborn screening test for isovaleric acidemia. Prompt follow-up of a positive newborn screening result for isovaleric acidemia is recommended [see *Warnings and Precautions* (5.7) and *Drug Interactions* (7.1)].

8.5 Geriatric Use
Of the total number of PIVVA-treated patients in the clinical trials, 66% were 65 years of age and older and 48% were 75 years of age and older in the PIVVA-treated patients evaluated for efficacy. A total of 19,579 (3%) of the PIVVA-treated patients evaluated for safety were 75 years of age and older. The maximum recommended daily human dose based on body surface area (BSA) is 185 mg/kg/day (approximately 10.2-fold higher than the maximum recommended daily human dose based on body surface area) [see *Adverse Reactions* (6.1)].
No overall differences in safety or effectiveness of PIVVA have been observed between patients 65 years of age and older and younger adult patients.
Meccillinam pharmacokinetics data from geriatric patients are not available. PIVVA is known to be substantially excreted by the kidneys, and geriatric patients are anticipated to have reduced renal function. The clinical significance of these changes on the safety and effectiveness of PIVVA is unknown. The available safety information does not suggest a need for dosage adjustment [see *Clinical Pharmacology* (12.3) and *Use in Specific Populations* (8.6)].
8.6 Renal Impairment
Reductions in systemic elimination as well as urinary excretion of meccillinam are anticipated with decreases in renal function. The clinical significance of these changes on the safety and effectiveness of PIVVA is unknown. The available safety information does not suggest a need for dosage adjustment [see *Clinical Pharmacology* (12.3)].

8.7 Pregnancy
8.7.1 Lactation
8.7.2 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Pivmecillinam is a pro-drug of meccillinam (the active antibacterial agent). Pivmecillinam is converted to meccillinam (the active antibacterial agent) and pivalic acid by non-specific esterases.
12.2 Pharmacodynamics
Like other beta-lactam antibiotic drugs, the bactericidal effect of PIVVA in the treatment of uUTI is dependent on time above minimum inhibitory concentration (MIC), which has been shown to best correlate with efficacy in animal models of infection against *E. coli*.
12.3 Pharmacokinetics
Pivmecillinam is a pro-drug of meccillinam (the active antibacterial agent). The pharmacokinetics of PIVVA in clinical trials from published studies is summarized in Table 2.
Table 2: Summary of Pharmacokinetic Parameters and Properties of Meccillinam in Healthy Females Receiving a Single Dose of 185 mg Pivmecillinam



Parameter	Value (Mean ± SD)
General Information	
Exposure (Day 1)	
C _{max} (mg/mL)	1.7 ± 1.1
AUC _{0-24h} (mg·min/mL)	214 ± 44
Accumulation	No clinically significant accumulation
Absorption	
Oral bioavailability of meccillinam*	25.59%
T _{max} (min)	90 ± 33
Effect of food	No clinically significant effect on Meccillinam PK
Distribution	
% plasma protein binding	<25%
Apparent volume of distribution (L)	51
Elimination	
Oral clearance (mL/min)	580 ± 100
Terminal half-life (min)	61 ± 32
Metabolism	
Metabolic pathways	• Pivmecillinam is converted to meccillinam (active antibacterial moiety) and pivalic acid by non-specific esterases. • Meccillinam undergoes minimal metabolism.
Excretion	
Major route of elimination	Urinary excretion - primarily as meccillinam (80% of dose)
C _{max} - maximum plasma concentration; AUC _{0-24h} - area under the plasma concentration-time curve from time zero to 24 hours; T _{max} - time to C _{max}	
*Bioavailability estimate based on comparison of dose-normalized mean exposure for 185 mg oral pivmecillinam administration and 200 mg following intravenous administration of meccillinam.	

Table 3: Composite Response Rates (Clinical Cure and Microbiological Response) at TOC in the uUTI Population

Trial	PIVVA (Clinical Cure and Microbiological Response)	Placebo (Clinical Cure and Microbiological Response)	Difference (95% CI)
Trial 1	PIVVA N=137, n (%)	Placebo N=134, n (%)	
Trial 2	PIVVA N=127, n (%)	Cephalexin N=132, n (%)	
Trial 3	PIVVA N=105, n (%)	Bupropfen N=119, n (%)	

Table 4: Clinical Cure Rates (Micro-TIT Population) at TOC in the uUTI Population

Trial	PIVVA (Clinical Cure Rates)	Placebo (Clinical Cure Rates)	Treatment Difference (95% CI)
Trial 1	PIVVA N=137, n (%)	Placebo N=134, n (%)	
Trial 2	PIVVA N=127, n (%)	Cephalexin N=132, n (%)	
Trial 3	PIVVA N=105, n (%)	Bupropfen N=119, n (%)	

Table 5: Microbiological Response Rates (Micro-TIT Population) at TOC in the uUTI Population

Trial	PIVVA (Microbiological Response Rates)	Placebo (Microbiological Response Rates)	Treatment Difference (95% CI)
Trial 1	PIVVA N=137, n (%)	Placebo N=134, n (%)	
Trial 2	PIVVA N=127, n (%)	Cephalexin N=132, n (%)	
Trial 3	PIVVA N=105, n (%)	Bupropfen N=119, n (%)	

16 HOW SUPPLIED/STORAGE AND HANDLING
PIVVA tablets are supplied as 185 mg pivmecillinam tablets, film-coated in child-resistant aluminum-aluminum push-through blisters.
Available pack sizes:
9 tablets (1 blister sheet with 9 tablets; NDC 62332-966-09, 50 tablets (5 blister sheets with 10 tablets per blister sheet) NDC 62332-966-10.
The tablet is white, circular, film-coated, debossed with "P" on one side and blank on the other. Approx. 9.5 mm in diameter.
16.2 Storage and Handling
Store PIVVA tablets at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store and dispense tablets in the unit-dose blister.

17 PATIENT COUNSELING INFORMATION
Hypersensitivity Reactions
Advise patients that allergic reactions, including serious allergic reactions, could occur with PIVVA and that serious reactions require immediate treatment. Ask patients about previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems, and other beta-lactam antibiotics. Advise the patient to call their healthcare provider immediately if they develop a new rash, urticaria, drug eruptions, swelling of the face, difficulty in breathing or other symptoms of allergic reactions [see *Warnings and Precautions* (5.1)].
Severe Cutaneous Adverse Reactions
Advise patients about the signs and symptoms of severe cutaneous adverse reactions. Advise the patient to discontinue PIVVA if they develop any type of skin rash, mucous lesions or any other sign of hypersensitivity and to seek immediate medical attention [see *Warnings and Precautions* (5.2)].
Drug Interactions
Advise patients to avoid use of valproic acid, valproate or other pivalate-generating drugs due to increased risk of carnitine depletion [see *Warnings and Precautions* (5.3)].
Diarrhea
Caution patients that diarrhea is a common problem caused by antibacterial drugs, including PIVVA, and that it usually ends when the drug is discontinued. Sometimes after starting therapy with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after taking the last dose of the drug. Advise patients to seek medical attention as soon as possible if this occurs [see *Warnings and Precautions* (5.5)].
Antibacterial Resistance
Patients should be counseled that antibacterial drugs including PIVVA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When PIVVA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by PIVVA or other antibacterial drugs in the future.
Interference with Newborn Screening Test
Advise patients that treatment of a pregnant individual with PIVVA prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening and prompt follow-up of a positive result is recommended [see *Warnings and Precautions* (5.7)].
Missed Doses
If a dose of PIVVA is missed, instruct patients to take the dose as soon as possible. Instruct patients not to double the dose to make up for the missed dose.
Manufactured by: APJ, Stringfins AB, Mariestadvägen 35, SE-645 41 Stringfins, Sweden
Manufactured for: Allergan Therapeutics, 550 Halls Drive, Suite 110 Bodminster, NJ 07921

Color:
Black