CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216483Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PIVYA™ safely and effectively. See full prescribing information for PIVYA.

PIVYA (pivmecillinam) tablets, for oral use
Initial U.S. Approval: 2024

---------- INDICATIONS AND USAGE----------

PIVYA is a penicillin class antibacterial 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)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PIVYA and other antibacterial drugs, PIVYA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of PIVYA is one 185 mg tablet orally 3 times a day for 3 to 7 days as clinically indicated. (2.1)
- Administer PIVYA with or without food. (2.1)

---------- DOSAGE FORMS AND STRENGTHS----------

Tablets: 185 mg pivmecillinam. (3)

---------- CONTRAINDICATIONS ----------

- Serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to PIVYA 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 PIVYA. If hypersensitivity reactions occur, discontinue treatment with PIVYA and institute appropriate therapy. (5.1)
- Severe Cutaneous Adverse Reactions (SCAR): Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with PIVYA. Monitor patients closely and discontinue PIVYA at the first signs or symptoms of SCAR or other signs of hypersensitivity. (5.2)
- Carnitine Depletion: Clinically significant hypocarnitinemia has been observed in patients at risk for reductions in serum carnitine. In patients with significant renal impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment, consider alternative antibacterial therapies. PIVYA is not recommended when prolonged antibacterial 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 PIVYA. Evaluate if diarrhea occurs (5.5)
- Interference with Newborn Screening Test: Treatment of a pregnant individual with PIVYA 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 ≥2% of the patients receiving PIVYA in clinical trials are nausea and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UTILITY therapeutics Ltd at 1-888-353-3180 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 4/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Uncomplicated Urinary Tract Infections

PIVYA 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 (E. coli)*, *Proteus mirabilis,* and *Staphylococcus saprophyticus.*

1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of PIVYA and other antibacterial drugs, PIVYA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of PIVYA is one 185 mg tablet orally 3 times a day for 3 to 7 days as clinically indicated. Administer PIVYA with or without food *[see Clinical Pharmacology (12.3)]*.

PIVYA (pivmecillinam) is a prodrug of mecillinam (the active antibacterial agent) *[see Clinical Pharmacology (12.3)]*.

2.2 Recommendations Regarding Missed Dose(s)

If a dose of PIVYA 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 DOSAGE FORMS AND STRENGTHS

Each film-coated tablet contains 185 mg pivmecillinam (equivalent to 200 mg pivmecillinam hydrochloride). 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

PIVYA is contraindicated in patients who have experienced a serious hypersensitivity reaction (e.g., anaphylaxis or Stevens-Johnson syndrome) to PIVYA or other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins) *[see Warnings and Precautions (5.1)]*.

4.2 Carnitine Deficiency

PIVYA 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

PIVYA is contraindicated in patients suffering from porphyria as pivmecillinam has been associated with acute attacks of 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 PIVYA *[see Adverse Reactions (6.1)]*. These reactions are more likely to occur in individuals with a history of penicillin, cephalosporin, or carbapenem hypersensitivity or a history of sensitivity to multiple allergens. Before initiating therapy with PIVYA, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems, and other beta-lactams because cross-hypersensitivity has been reported. PIVYA is contraindicated in patients who have experienced a serious hypersensitivity reaction *[see Contraindications (4.1)]*. If an allergic reaction occurs, discontinue PIVYA and institute appropriate therapy.

5.2 Severe Cutaneous Adverse Reactions

Severe Cutaneous Adverse Reactions (SCAR) including Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported with PIVYA *[see Adverse Reactions (6.2)]*. Monitor patients closely and discontinue PIVYA 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 PIVYA. Symptoms of carnitine depletion include hypoglycemia, muscle aches, fatigue, and confusion. PIVYA is contraindicated in patients with primary or secondary carnitine deficiency due to 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 PIVYA. Clinically significant hypocarnitinemia has been observed in patients receiving long term treatment with pivmecillinam. PIVYA is not recommended when prolonged antibacterial treatment is necessary. The effects on carnitine concentrations of repeated short-term courses of PIVYA are not known. In patients at risk for reductions in serum carnitine (e.g., patients with significant renal impairment or decreased muscle mass consider alternative antibacterial

therapies. Avoid concurrent treatment with valproic acid, valproate or other pivalate-generating drugs due to increased risk of carnitine depletion *[see Drug Interaction (7.1)]*.

5.4 Acute Porphyria

PIVYA is contraindicated in patients suffering from porphyria as pivmecillinam has been associated with acute attacks of porphyria *[see Contraindications (4.3)]*. These episodes may be life-threatening, and include symptoms and signs such as anxiety, confusion, limb or abdominal pain, hyponatremia, seizures, and muscle weakness.

5.5 *Clostridioides difficile*-Associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including PIVYA, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial drugs alters the normal flora of the colon and may permit overgrowth of *C. difficile.*

C. difficile produces toxins A and B that contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplement, antibacterial drug treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

5.6 Development of Drug-Resistant Bacteria

Prescribing PIVYA in the absence of a proven or strongly suspected bacterial infection or for prophylaxis is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.7 Interference with Newborn Screening Test

Treatment of a pregnant individual with PIVYA 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.

6 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 PIVYA was evaluated in 579 adult female patients with uUTI who received PIVYA at a dose of 185 mg three times daily, or at higher daily doses (not approved for PIVYA) for 3 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 91 years of age.

No serious adverse reactions were reported in patients treated with PIVYA in the trials.

In Trial 1, the most common adverse reactions observed in ≥2% of the patients receiving PIVYA included nausea (4.3%) and diarrhea (2.1%).

In Trial 2 and Trial 3, the most common adverse reaction occurring in ≥1% of patients receiving PIVYA was nausea with an incidence of 1.4% in Trial 2 and 3.6% in Trial 3.

Table 1 lists the most frequently reported adverse reactions occurring in ≥1% of patients receiving PIVYA in Trial 1.

Table 1: Adverse Reactions Occurring in ≥1% of Patients Receiving PIVYA in Trial 1

Adverse Reactions (AR)	PIVYA* N=282 n (%)	Placebo N=288 n (%)
Nausea	12 (4.3)	6 (2.1)
Diarrhea	6 (2.1)	2 (0.7)
Vulvovaginal candidiasis	5 (1.8)	0
Genital pruritus	5 (1.8)	4 (1.4)
Headache	4 (1.4)	1 (0.3)

*PIVYA 185 mg three times per day for 7 days

Selected adverse reactions occurring in ≤1% of patients who received PIVYA in the clinical trials were vomiting, rash, dyspepsia, and abdominal pain.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of pivmecillinam outside of the United States. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorder: Thrombocytopenia
Ear and labyrinth disorder: Vertigo

Gastrointestinal disorders: Esophageal ulcer, esophagitis, mouth ulceration
Hepatobiliary disorders: Hepatic function abnormal
Immune system disorders: Anaphylactic reaction, Angioedema
Infections and infestations: Clostridioides difficile-associated diarrhea
Metabolism and nutrition disorders: Carnitine decreased
Nervous system disorders: Dizziness
Skin and subcutaneous tissue disorders: Urticaria, pruritus, 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)

7 DRUG INTERACTIONS

7.1 Other Pivalate-Generating Drugs

Avoid concurrent treatment with valproic acid, valproate, or other pivalate-generating drugs. If concomitant use with PIVYA is necessary, counsel patients to monitor adverse reactions associated with carnitine depletion (e.g., hypoglycemia, muscle aches, fatigue, and confusion) *[see Warnings and Precautions (5.3)]*.

Pivmecillinam is a pivalate-generating prodrug *[see Clinical Pharmacology (12.3)]*. Pivalate can be activated to a coenzyme-A thioester in cells which is further converted to pivaloylcarnitine and excreted in urine. Pivalate elimination associated with concomitant use of pivmecillinam with other pivalate-generating drugs decreases carnitine concentrations in plasma which may increase the risk of carnitine depletion-associated adverse reactions *[see Warnings and Precautions (5.3)]*.

7.2 Methotrexate

Clearance of methotrexate from the body can be reduced by concurrent use of drugs in the penicillin class, including PIVYA. Where possible, consider alternative therapy.

7.3 Drug Interference with Newborn Screening Test

Treatment of a pregnant individual with PIVYA 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Published observational studies on PIVYA use during the first trimester do not indicate an increased risk of major birth defects *(see Data)*. There are limited studies on PIVYA use during pregnancy that evaluate the risk of miscarriage and other adverse maternal or fetal outcomes. These studies have methodological limitations hindering interpretation. No dose adjustment is required in pregnant women *(see Clinical Considerations)*.

Developmental toxicity studies with pivmecillinam or mecillinam administered during organogenesis to rats and mice showed no evidence of embryo-fetal toxicity, including drug-induced fetal malformations, at doses approximately 3.4 or 7.9 times (rats) or 5.1 or 3.9 times (mice) higher than given to patients receiving the maximum recommended daily dose. Evidence of slight fetotoxicity (reduced ossification) was seen in offspring of rats that were given pivmecillinam during organogenesis at a dose approximately 10.2-fold higher than the maximum recommended daily human dose *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Interference with Newborn Screening Test

Treatment of a pregnant individual with PIVYA prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening *[see Warnings and Precautions (5.7) and Drug Interactions (7.3)]*.

Dose Adjustments During Pregnancy and the Postpartum Period

No dosage adjustment is recommended for pregnant females *(see Data)*.

Data

Human data

Two cohort studies in 42,223 pregnant women who were exposed to PIVYA during the first trimester did not observe an increased risk of major birth defects when compared to 50,099 pregnant women exposed to other antibacterial drugs. These two studies were limited by potential exposure misclassification.

No clinically significant differences in mecillinam C_{max} and AUC were observed in pregnant adult women (10 to 32 weeks gestation) administered PIVYA 185 mg orally in a published study.

Animal data

Pivmecillinam administered during the period of organogenesis (gestation days 6-15) had no adverse effects on embryofetal development in rats or mice at oral doses up to 194 mg/kg/day in rats and 582 mg/kg/day in mice. These doses are approximately 3.4-fold and 5.1-fold higher than the maximum recommended daily human dose based on body surface area, respectively. There was a skeletal variation (reduced ossification of sternebrae, possibly indicating slight fetotoxicity) in offspring of rats treated at 582 mg/kg/day (approximately 10.2-fold higher than the maximum recommended daily human dose based on body surface area). Mecillinam did not cause adverse effects on embryofetal development in rats and mice when administered by subcutaneous injection at doses up to 450 mg/kg/day (approximately 7.9-fold and 3.9-fold higher

than the maximum recommended daily human dose based on body surface area, respectively). In pre- and postnatal studies in rats where maternal animals were dosed beginning during gestation (Day 15) and continuing throughout the weaning period, neither pivmecillinam nor mecillinam had adverse effects on the maternal animals or on the survival and development of the offspring. Pivmecillinam was given orally at doses up to 582 mg/kg/day and mecillinam was given subcutaneously at doses up to 450 mg/kg/day (approximately 10.2-fold and 7.9-fold higher than the maximum recommended daily human dose of PIVYA, based on body surface area, respectively).

8.2 Lactation

Risk Summary

There are insufficient data to exclude the presence of mecillinam in human milk. Mecillinam is present in animal milk *(see Data)*. When a drug is present in animal milk, it is likely to be present in human milk. There are pharmacovigilance reports of adverse reactions with mecillinam exposure in breastfed infants, including rash and diarrhea. There are no data on the effects of mecillinam on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother`s clinical need for PIVYA and any potential adverse effects on the breastfed child from PIVYA or from the underlying maternal condition.

Data

In a study of lactating cows given 8 mg/kg mecillinam 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 mecillinam in animal milk does not necessarily predict the concentration of drug in human milk.

8.4 Pediatric Use

The safety and effectiveness of PIVYA have not been established in pediatric patients.

Carnitine Depletion

Symptomatic hypocarnitinemia 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 been observed. PIVYA is not recommended when prolonged antibacterial treatment is necessary *[see Warnings and Precautions (5.3)]*. PIVYA is contraindicated in patients with primary or secondary carnitine deficiency *[see Contraindications (4.2)]*.

Interference with Newborn Screening Test

Newborns exposed to PIVYA *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 (7.3)]*.

8.5 Geriatric Use

Of the total number of PIVYA-treated patients in the clinical trials evaluated for safety, 80/579 (14%) were 65 years of age and older, and 48/369 (13%) were 65 years of age and older in the PIVYA-treated patients evaluated for efficacy. A total of 19/579 (3%) of the PIVYA-treated patients evaluated for safety were 75 years of age and older and 12/369 (3%) were 75 years of age and older in the PIVYA-treated patients evaluated for efficacy *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

No overall differences in safety or effectiveness of PIVYA have been observed between patients 65 years of age and older and younger adult patients.

Mecillinam pharmacokinetics data from geriatric patients are not available. PIVYA 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 efficacy or safety 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)]*.

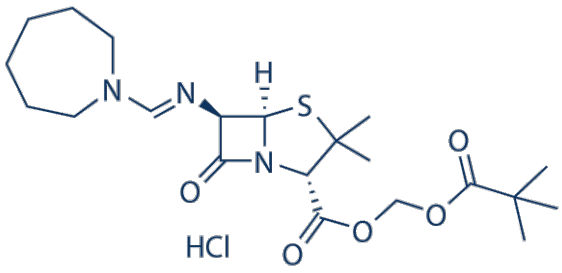
8.6 Renal Impairment

Reductions in systemic elimination as well as urinary excretion of mecillinam are anticipated with decreases in renal function. The clinical significance of these changes on efficacy is unknown. The available safety information does not suggest a need for dosage adjustment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

PIVYA tablets contain pivmecillinam (as pivmecillinam hydrochloride), a penicillin class antibacterial for oral administration. The chemical name of pivmecillinam hydrochloride is methylene 2,2-dimethylpropanoate (2S,5R,6R)-6-[[(hexahydro-1H-azepin-1-yl)methylene]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate hydrochloride. The molecular formula for pivmecillinam hydrochloride is $C_{21}H_{33}N_3O_5S \cdot HCl$. The molecular weight of pivmecillinam hydrochloride is 476.0 g/mol.

Figure 1: Chemical Structure of Pivmecillinam Hydrochloride



Each film-coated PIVYA tablet for oral administration contains 185 mg pivmecillinam (equivalent to 200 mg pivmecillinam hydrochloride), and the following inactive ingredients: cellulose microcrystalline, hydroxypropyl cellulose, hypromellose, magnesium stearate, paraffin, and simethicone.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PIVYA is an antibacterial drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Like other beta-lactam antibacterial drugs, the bacteriological effect of PIVYA 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 mecillinam (the active antibacterial moiety). The pharmacokinetic information for mecillinam from published studies is summarized in Table 2.

Table 2: Summary of Pharmacokinetic Parameters and Properties of Mecillinam in Healthy Females Receiving a Single Dose of 185 mg Pivmecillinam

Parameter	Value (Mean ± SD)
General Information	
Exposure (Day 1)	
C_{max} (mcg/mL)	1.7 ± 1.1
$AUC_{0\text{-}8\ hours}$ (mcg·min/mL)	214 ± 44
Accumulation	No clinically significant accumulation
Absorption	
Oral bioavailability of mecillinam*	25-35%
T_{max} (min)	90 ± 33
Effect of food	No clinically significant effect on Mecillinam 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 mecillinam (active antibacterial moiety) and pivalic acid by non-specific esterases. • Mecillinam undergoes minimal metabolism.
Excretion	
Major route of elimination	Urinary excretion , primarily as mecillinam (80% of dose)

C_{max}=maximum plasma concentration; $AUC_{0\text{-}8\ hours}$=area under the plasma concentration-time curve from time zero to 8 hours;T_{max}=time to C_{max}
*Bioavailability estimate based on comparison of dose normalized mecillinam exposure after 185 mg oral pivmecillinam administration and 200 mg IV mecillinam.
†Excretion estimate based on PK data following intravenous administration of mecillinam.

Specific Populations

The effect of age, sex, race and body weight on pivmecillinam or mecillinam pharmacokinetics is unknown.

Patients with Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of mecillinam have not been evaluated. Hepatic impairment is not expected to alter the elimination of mecillinam as hepatic metabolism/excretion represents a minor pathway of elimination for mecillinam. Dosage adjustments are not necessary in patients with impaired hepatic function.

Patients with Renal Impairment

In published pharmacokinetic studies, mecillinam systemic elimination and urinary excretion decreases with degree of renal function.

Drug Interaction Studies

Clinical Studies

OAT1/3 inhibitors: Mean mecillinam C_{max} increased by approximately 80% and AUC by approximately 40% following concomitant use of oral probenecid (OAT1/3 inhibitor) with pivmecillinam in two published studies.

MATE1 or MATE2K inhibitors: The effect of concomitant use on pivmecillinam or mecillinam pharmacokinetics is unknown.

In Vitro Studies Where Drug Interaction Potential Was Not Further Evaluated Clinically

Cytochrome P450 (CYP) enzymes: Mecillinam does not inhibit nor induce CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

Transporter systems: Mecillinam is a substrate of the renal transporters organic anion transporter-3 (OAT3), multidrug and extrusion protein-1 (MATE1), multidrug and extrusion protein-2K (MATE2-K). Mecillinam does not inhibit breast cancer resistance protein (BCRP), P-glycoprotein (PgP), MATE1, MATE2-K, organic anion transporter-1 (OAT1), OAT3, organic anion transporting polypeptides -1B1 and 1B3 (OATP1 B1/B3) and organic cation transporter-2 (OCT2) drug transporters.

12.4 Microbiology

Mechanism of Action

Pivmecillinam is the pro-drug containing the pivaloyloxymethylester of the amidinopenicillanic acid, mecillinam. Orally administered, pivmecillinam is well absorbed and subsequently rapidly hydrolyzed to mecillinam, the active antibacterial agent, by non-specific esterases present in blood, gastrointestinal mucosa and other tissues. Mecillinam is a beta-lactam antibacterial drug with a targeted spectrum of activity. It is mainly active against gram-negative bacteria and works by interfering with the biosynthesis of the bacterial cell wall. Unlike the majority of other beta-lactam agents, which preferentially bind gram-negative PBP-1A, -1B or -3, mecillinam exerts high specificity against penicillin-binding protein-2 (PBP-2) in the gram-negative cell wall.

Resistance

Mecillinam demonstrated in vitro activity against Enterobacterales in the presence of some beta-lactamases and extended-spectrum beta-lactamases (ESBL) of the following groups: CTX-M, SHV, TEM and AmpC.

The inhibitory action of mecillinam on PBP-2 results in low cross-resistance with certain beta-lactams. The frequency of resistance to mecillinam in *E. coli* range from 8×10^{-8} to 2×10^{-5} when exposed to 32-256 times MIC.

Interaction With Other Antimicrobials

PIVYA has demonstrated synergy with other beta-lactams. *In vitro* antagonism has been shown with nitrofurantoin.

Antimicrobial Activity

PIVYA has been shown to be active against most isolates of the following microorganisms both in vitro and in clinical infections *[see Indications and Usage (1)]*.

Aerobic Bacteria

Gram-negative Bacteria

- *Escherichia coli*
- *Proteus mirabilis*

Gram-positive Bacteria

- *Staphylococcus saprophyticus*

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for PIVYA against isolates of similar genus or organism group. However, the efficacy of PIVYA in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic Bacteria

Gram-negative Bacteria

- *Citrobacter freundii*
- *Enterobacter cloacae*
- *Klebsiella pneumoniae*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with pivmecillinam or mecillinam.

Mutagenesis

Pivmecillinam was mutagenic in the Ames bacterial reverse mutation assay. Pivmecillinam induced chromosome breaks in cultured human lymphocytes, but did not induce damage to mouse bone marrow cell chromosomes in vivo. The positive findings observed in the in vitro studies are considered to be due to the release of formaldehyde from the pivoxil ester moiety of pivmecillinam because they were not observed when mecillinam was tested in the same assays. The positive findings are not considered relevant to the clinical use of PIVYA because the small amount of formaldehyde released is eliminated quickly in vivo, but not in vitro.

Impairment of Fertility

Mecillinam had no adverse effect on fertility in male or female rats at subcutaneous doses up to 450 mg/kg/day (approximately 7.9-fold higher than the maximum recommended daily human dose based on body surface area). Pivmecillinam had no adverse effect on fertility in male or female rats at oral doses up to 582 mg/kg/day (approximately 10.2-fold higher than the maximum recommended daily human dose based on body surface area).

14 CLINICAL STUDIES

Three controlled clinical trials comparing different PIVYA dosing regimens to placebo (Trial 1), to another oral antibacterial drug (Trial 2), or to ibuprofen (Trial 4) evaluated the efficacy of pivmecillinam for the treatment of uUTI. Efficacy was assessed in the Microbiological Intent-to-Treat (micro-ITT) population which included all randomized subjects with a positive baseline urine culture defined as $\geq 10^5$ colony-forming-units (CFU)/mL of a uropathogen where CFU count was available and no more than 2 species of microorganisms, regardless of colony count, and no baseline pathogen was non-susceptible to the active comparator. The composite response rates (composite endpoint of clinical cure and microbiological response), as well as clinical cure and microbiological response rates of the recommended 185 mg three times daily dosing regimen are summarized in Table 3, Table 4 and Table 5.

Trial 1 was a multi-center, randomized, double-blinded study in Sweden evaluating the efficacy of 3 dosage regimens of PIVYA tablets (185 mg three times daily for 7 days, 185 mg two times daily for 7 days (not an approved dosing regimen for PIVYA), and 370 mg two times daily for 3 days (not an approved dosing regimen for PIVYA)) compared to placebo in women 18 years of age or older with symptoms of uUTI. The trial enrolled patients with mean age of 45 years with *E. coli* as the most common baseline pathogen. PIVYA demonstrated efficacy for the composite response of clinical cure and microbiological response at Day 8-10. Clinical cure was defined as no persisting symptoms during and post-therapy. Microbiological response for the initial pathogen at follow-up visits was defined as reduction in the number of bacteria to $<10^3$ CFU/mL. Composite response was achieved in 85/137 (62%) of patients in the PIVYA group and 14/134 (10%) in the placebo group at TOC in the micro-ITT population.

Trial 2 was a multi-center, randomized, double-blinded study in the U.S. evaluating the efficacy and safety of PIVYA tablets 185 mg three times a day for 3 days compared to cephalexin 250 mg four times daily for 7 days in females 18 years of age or older with uUTI. The trial enrolled patients with a mean age of 31 years, who were 85% White and 12% Black or African American with *E. coli* as the most common baseline pathogen. Clinical cure was defined as no persisting symptoms during and post-therapy. Microbiological response was defined as negative urine culture ($<10^3$ CFU/mL) for the initial pathogen at Day 10. Composite response was achieved in 91/127 (72%) of patients in the PIVYA group and 100/132 (76%) in the cephalexin group at the TOC in the micro-ITT population.

Trial 4 (NCT01849926) was a multi-center, randomized, double-blinded, non-inferiority study in Denmark, Norway, and Sweden to evaluate the efficacy and safety of PIVYA tablets 185 mg three times daily for 3 days compared to ibuprofen 600 mg three times daily for 3 days in women 18 to 60 years of age with clinical symptoms of uUTI. The trial enrolled patients with mean age of 29 years with *E. coli* as the most common baseline pathogen. PIVYA demonstrated efficacy for the composite response (clinical cure and microbiological response) at TOC (Day 14). Clinical cure was defined as the patient reporting no symptoms at Day 7 and reporting no symptoms at Day 14. Microbiological response was defined as negative urine culture ($<10^3$ CFU/mL) for the initial pathogen at Day 14. Composite response was achieved in 69/105 (66%)

in the PIVYA group and 26/119 (22%) in the ibuprofen group at TOC in the micro-ITT population.

Table 3: **Composite Response Rates (Clinical Cure and Microbiological Response) at TOC in the uUTI trials (Micro-ITT Population)**

	Composite Response Rates (Clinical Cure and Microbiological Response)		
Trial 1	PIVYA N=137, n (%)	Placebo N=134, n (%)	Difference (95% CI)
	85 (62)	14 (10)	52 (41, 62)
Trial 2	PIVYA N=127, n (%)	Cephalexin N=132, n (%)	
	91 (72)	100 (76)	-4 (-16, +7)
Trial 4	PIVYA N=105, n (%)	Ibuprofen N=119, n (%)	
	69 (66)	26 (22)	44 (31, 57)

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

	Clinical Cure Rates		
Trial 1	PIVYA N=137, n (%)	Placebo N=134, n (%)	Treatment Difference (95% CI)
	87 (64)	31 (23)	40 (29, 52)
Trial 2	PIVYA N=127, n (%)	Cephalexin N=132, n (%)	
	105 (83)	112 (85)	-2 (-12, +8)
Trial 4	PIVYA N=105, n (%)	Ibuprofen N=119, n (%)	
	81 (77)	45 (38)	39 (27, 52)

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

	Microbiological Response Rates		
Trial 1	PIVYA N=137, n (%)	Placebo N=134, n (%)	Treatment difference (95% CI)
	119 (87)	35 (26)	61 (51,71)
Trial 2	PIVYA N=127, n (%)	Cephalexin N=132, n (%)	
	97 (76)	106 (80)	-4 (-15, +7)
Trial 4	PIVYA N=105, n (%)	Ibuprofen N=119, n (%)	
	78 (74)	64 (54)	21 (7, 34)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

PIVYA 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 82456-200-09.

50 tablets (5 blister sheets with 10 tablets per blister sheet) NDC 82456-200-50.

The tablet is white, circular, film-coated, debossed with “P” on one side and blank on the other . Size: Approx. 9.5 mm in diameter.

16.2 Storage and Handling

Store PIVYA tablets at 20ºC to 25ºC (68ºF to 77ºF); 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 blisters.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Advise patients that allergic reactions, including serious allergic reactions, could occur with PIVYA and that serious reactions require immediate treatment. Ask patients about previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems, and other beta-lactam antibacterials. 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 PIVYA if they develop any type of skin rash, mucosal 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

Counsel patients that diarrhea is a common problem caused by antibacterial drugs, including PIVYA, and it usually ends when the drug is discontinued. Sometimes after starting treatment 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 PIVYA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When PIVYA 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 PIVYA or other antibacterial drugs in the future.

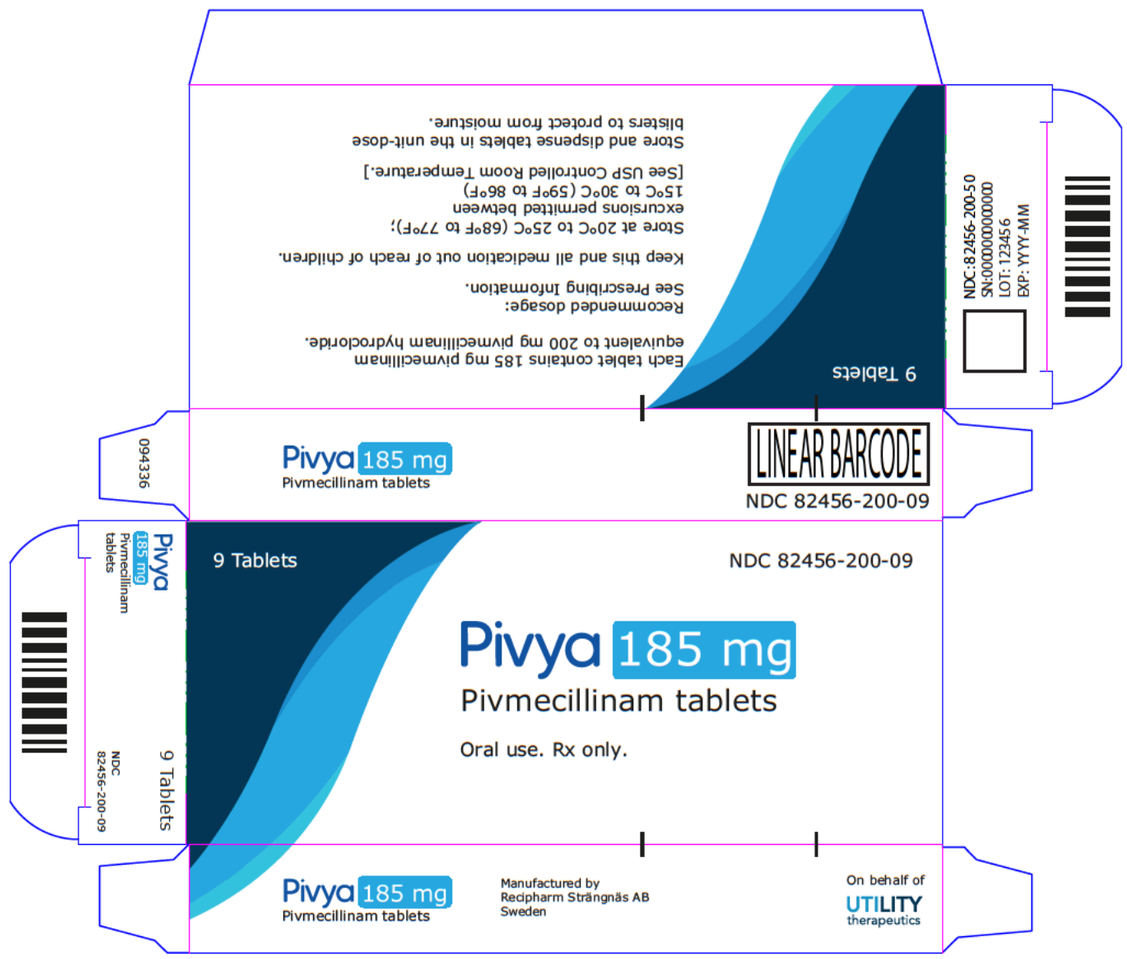
Interference with Newborn Screening Test

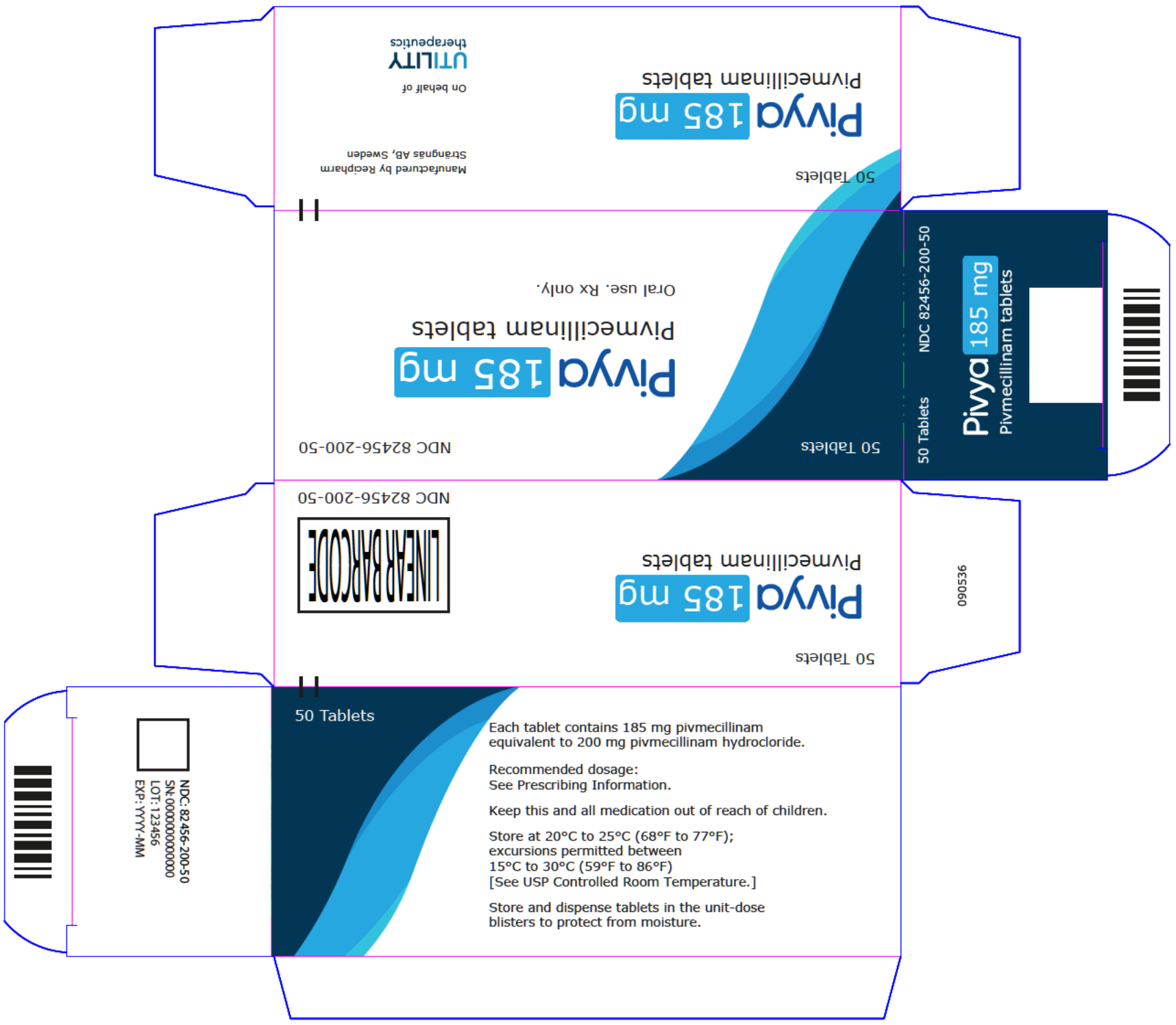
Advise patients that treatment of a pregnant individual with PIVYA prior to delivery may cause a false positive test for isovaleric acidemia in the newborn as part of newborn screening and prompt follow-up of a positive result is recommended *[see Warnings and Precautions (5.7)]*.

Missed Doses

If a dose of PIVYA 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 for: UTILITY therapeutics Ltd, UK
Manufactured by: Recipharm Strängnäs AB, Mariefredsvägen 35, S-645 41 Strängnäs, Sweden
Distributed by : UTILITY therapeutics Ltd, 1 Shetland Road, Florham Park, NJ. 07932


Pivya 185 mg
Pivmecillinam tablets
9 Tablets
NDC 82456-200-09
Pivya 185 mg
Pivmecillinam tablets
Oral use. Rx only.
Manufactured by
Recipharm Strängnäs AB
Sweden
On behalf of
UTILITY
therapeutics
Pivya 185 mg
Pivmecillinam tablets
9 Tablets
NDC 82456-200-09
LINEAR BARCODE
Pivya 185 mg
Pivmecillinam tablets
094336
9 Tablets
Each tablet contains 185 mg pivmecillinam
equivalent to 200 mg pivmecillinam hydrochloride.
Recommended dosage:
See Prescribing Information.
Keep this and all medication out of reach of children.
Store at 20°C to 25°C (68°F to 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
blisters to protect from moisture.
NDC:82456-200-50
SN:0000000000000
LOT: 123456
EXP: YYYY-MM


Pivya 185 mg
Pivmecillinam tablets
50 Tablets
NDC 82456-200-50
Oral use. Rx only.
Manufactured by Reciparm
Strängnäs AB, Sweden
On behalf of
UTILITY
therapeutics
090536
LINEAR BARCODE
NDC: 82456-200-50
SN: 000000000000
LOT: 123456
EXP: YYYY-MM
Each tablet contains 185 mg pivmecillinam
equivalent to 200 mg pivmecillinam hydrocloride.
Recommended dosage:
See Prescribing Information.
Keep this and all medication out of reach of children.
Store at 20°C to 25°C (68°F to 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
blisters to protect from moisture.

NDC 82456-200-09

Pivya 185 mg
pivmecillinam tablet
Mfg. by Recipharm
Strängnäs AB
EXP YYYY-MM
LOT 123456
LINEAR BAR CODE

022833

NDC 82456-200-50

Pivya 185 mg
pivmecillinam tablet
Mfg. by Recipharm
Strängnäs AB
EXP YYYY-MM
LOT 123456
LINEAR BAR CODE

022033

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER W KIM
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