**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use ORLYNVAH™ safely and effectively. See full prescribing information for ORLYNVAH™.**

**ORLYNVAH™ (sulopenem etzadroxil and probenecid) tablets, for oral use**
**Initial U.S. Approval: 2024**

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

ORLYNVAH a combination of sulopenem etzadroxil, a penem antibacterial, and probenecid, a renal tubular transport inhibitor, is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options. (1.1)

Limitations of Use

ORLYNVAH is not indicated for the treatment of:

- Complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI. (1.1, 14.2)
- Complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI. (1.1, 14.3)

Usage to Reduce Development of Drug-Resistant Bacteria

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORLYNVAH and other antibacterial drugs, ORLYNVAH should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy. (1.2, 5.5)

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

- The recommended dosage of ORLYNVAH is one tablet orally twice daily for 5 days. (2.1)
- Administration of ORLYNVAH with food is recommended. (2.1)

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

- ORLYNVAH Tablets: 500 mg sulopenem etzadroxil and 500 mg probenecid. (3)

----------**CONTRAINDICATIONS**----------

- Patients with a history of hypersensitivity to the components of ORLYNVAH (sulopenem etzadroxil and probenecid) or other beta-lactam antibacterial drugs. (4)
- Patients with known blood dyscrasias. (4)
- Patients with known uric acid kidney stones. (4)
- Concomitant use of ORLYNVAH and ketorolac tromethamine is contraindicated. (4)

----------**WARNINGS AND PRECAUTIONS**----------

- Hypersensitivity Reactions: Hypersensitivity reactions have been reported in patients treated with ORLYNVAH. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, have been reported with beta-lactam antibacterial drugs. Severe allergic reactions and anaphylaxis have been reported with the use of probenecid (a component of ORLYNVAH). If an allergic reaction to ORLYNVAH occurs, discontinue the drug and institute appropriate therapy. (5.1)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): This has been reported with nearly all systemic antibacterial agents. Evaluate if diarrhea occurs. (5.2)
- Exacerbation of Gout: When prescribing ORLYNVAH to patients with a known history of gout, ensure appropriate therapy of gout is instituted. (5.4)

----------**ADVERSE REACTIONS**----------

The most common adverse reactions (≥2%) in patients treated with ORLYNVAH were diarrhea, nausea, vulvovaginal mycotic infection, headache, and vomiting. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Iterum Therapeutics. at 1-866-414-SULO or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

----------**DRUG INTERACTIONS**----------

- Ketoprofen: Concomitant use is not recommended (7.1)
- See full prescribing information for additional clinically significant drug interactions with ORLYNVAH (7.1)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 10/2024**

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

### 1.1 Uncomplicated Urinary Tract Infections

ORLYNVAH is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

Limitations of Use
ORLYNVAH is not indicated for the treatment of:

- Complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI *[see Clinical Studies (14.2)]*.
- Complicated intra-abdominal infections (cIAI)) or as step-down treatment after intravenous antibacterial treatment of cIAI *[see Clinical Studies (14.3)]*.

### 1.2 Usage to Reduce Development of Drug-Resistant Bacteria

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORLYNVAH and other antibacterial drugs, ORLYNVAH should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy *[see Warnings and Precautions (5.5)]*.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dosage

The recommended dosage of ORLYNVAH is one tablet (sulopenem etzadroxil 500 mg and probenecid 500 mg) orally twice daily for 5 days. Administration of ORLYNVAH with food is recommended *[see Clinical Pharmacology (12.3)]*.

### 2.2 Recommended Dosage in Patients with Renal Impairment

Administration of ORLYNVAH is not recommended in patients with creatinine clearance (CrCL) less than 15 mL/min or patients on hemodialysis. No dosage adjustment is required for ORLYNVAH in patients with CrCL greater than or equal to15 mL/min *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

### 2.3 Recommendations Regarding Missed Dose(s)

If a dose of ORLYNVAH 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

ORLYNVAH (sulopenem etzadroxil 500 mg and probenecid 500 mg) tablets are supplied as pink, oval-shaped, film-coated, fixed-dose, bilayer combination tablets debossed with SULO on one side and plain on the other side.

## 4 CONTRAINDICATIONS

ORLYNVAH is contraindicated in patients with:

- A history of hypersensitivity to the components of ORLYNVAH (sulopenem etzadroxil and probenecid) or other beta-lactam antibacterial drugs *[see Warnings and Precautions (5.1)]*

- Known blood dyscrasias
- Known uric acid kidney stones *[see Warnings and Precautions (5.3)]*

Concomitant use of ORLYNVAH and ketorolac tromethamine is contraindicated *[see Drug Interactions (7.1)]*

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Hypersensitivity Reactions

Hypersensitivity reactions, specifically cases of angioedema, have been reported in patients treated with ORLYNVAH *[see Adverse Reactions (6.1)]*. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs *[see Contraindications (4)]*. Before therapy with ORLYNVAH is instituted, carefully inquire about previous hypersensitivity reactions to other carbapenems, cephalosporins, penicillins, or other beta-lactams because cross-hypersensitivity among beta-lactam antibacterial drugs has been reported. Severe allergic reactions and anaphylaxis have been reported with the use of probenecid (a component of ORLYNVAH). If an allergic reaction to ORLYNVAH occurs, discontinue the drug and institute appropriate supportive measures.

### 5.2 *Clostridioides difficile*-Associated Diarrhea

*Clostridioides difficile*-associated diarrhea (CDAD) has been reported in users of nearly all systemic antibacterial drugs with severity ranging from mild diarrhea to fatal colitis. Treatment with antibacterial agents can alter the normal flora of the colon and may permit overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial 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 more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible. Appropriate measures such as fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

### 5.3 Risk of Uric Acid Kidney Stone Development

When prescribing ORLYNVAH to patients with a history of gout, appropriate measures to reduce the risk of uric acid kidney stone development should be instituted, such as increased fluid intake and alkalization of the urine. ORLYNVAH is contraindicated in patients with known uric acid kidney stones.

### 5.4 Exacerbation of Gout

ORLYNVAH may cause exacerbation of gout. When prescribing ORLYNVAH to patients with a known history of gout, ensure appropriate therapy of gout is instituted.

### 5.5 Development of Drug-Resistant Bacteria

Prescribing ORLYNVAH in the absence of a proven or strongly suspected susceptible uUTI is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria *[see Indications and Usage (1.2)]*.

## 6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in the Warnings and Precautions section.

- Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- *Clostridioides difficile*-Associated Diarrhea *[see Warnings and Precautions (5.2)]*
- Risk of Uric Acid Kidney Stone Development *[see Warnings and Precautions (5.3)]*
- Exacerbation of Gout *[see Warnings and Precautions (5.4)]*

## 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 rates observed in practice.

ORLYNVAH was evaluated in two Phase 3 controlled, multinational, randomized, double blind, double dummy clinical trials (Trial 1 and Trial 2) in adult women with uUTI. Therapy with oral ORLYNVAH tablets was administered as one tablet twice daily for 5 days *[see Clinical Studies (14)]*. The trials included 1932 patients treated with ORLYNVAH and 1929 patients treated with comparator antibacterial drugs (ciprofloxacin or amoxicillin/clavulanate). The median age of patients treated with ORLYNVAH was 50 years, ranging between 18 and 91 years old. Patients treated with ORLYNVAH were all female (100%), predominantly White (83%) and from the United States (83%).

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

Serious adverse reactions occurred in 6/1932 (0.3%) of uUTI patients treated with ORLYNVAH and in 2/822 (0.2%) and 5/1107 (0.5%) of patients treated with ciprofloxacin or amoxicillin/clavulanate, respectively. Treatment discontinuation due to an adverse reaction occurred in 21/1932 (1%) of patients treated with ORLYNVAH, 8/822 (1%) of patients treated with ciprofloxacin, and 4/1107 (0.4%) of patients treated with amoxicillin/clavulanate. The most commonly reported adverse reactions leading to discontinuation of ORLYNVAH were nausea (6/1932; 0.3%), diarrhea (5/1932; 0.3%), as well as abdominal pain, gastroesophageal reflux disease, vomiting, and dizziness, each 0.2% (3/1932).

Most Common Adverse Reactions

Adverse reactions occurring at 2% or greater in patients receiving ORLYNVAH were diarrhea, nausea, vulvovaginal mycotic infection, headache, and vomiting.

Table 1 lists adverse reactions reported in ≥ 1% of patients receiving ORLYNVAH in the phase 3 uUTI trials (Trial 1 and Trial 2). The most common adverse reactions in patients treated with ORLYNVAH were diarrhea (10%) and nausea (4%).

**Table 1. Adverse Reactions Occurring in ≥ 1% of Patients Receiving ORLYNVAH in the Uncomplicated Urinary Tract Infection Clinical Trials (Trial 1 and Trial 2)**

| Adverse Reaction | ORLYNVAH[a] N=1932 n (%) | Amoxicillin/Clavulanate[b] N=1107 n (%) | Ciprofloxacin[c] N=822 n (%) |
|---|---|---|---|
| Diarrhea[1] | 194 (10) | 45 (4) | 21 (3) |
| Nausea | 80 (4) | 32 (3) | 30 (4) |
| Vulvovaginal mycotic infection[2] | 46 (2) | 13 (1) | 7 (1) |
| Headache | 42 (2) | 17 (2) | 18 (2) |
| Vomiting | 29 (2) | 4 (0.4) | 11 (1) |
| Abdominal pain[3] | 22 (1) | 11 (1) | 9 (1) |

[a] ORLYNVAH tablets (sulopenem etzadroxil 500mg / probenecid 500mg) 1 tablet twice daily for 5 days; [b]Amoxicillin/clavulanate tablets (875 mg /125 mg) 1 tablet twice daily for 5 days [c]Ciprofloxacin tablets (250 mg) 1 tablet twice daily for 3 days.
[1] Diarrhea includes diarrhea and loose stools.
[2] Vulvovaginal mycotic infection includes vulvovaginal mycotic infection, vulvovaginal candidiasis, vaginal infection, fungal infection, genital infection fungal, and yeast infection.
[3]Abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal discomfort.

Other Adverse Reactions of ORLYNVAH

The following selected adverse reactions were reported in the ORLYNVAH-treated patients at a rate of <1% in the uUTI Trial 1 and Trial 2:

*Cardiac disorders:* tachycardia
*Ear and labyrinth disorders:* vertigo
*Gastrointestinal disorders:* abdominal distension, abnormal feces, constipation, dry mouth, dyspepsia, eructation, feces discolored, feces soft, flatulence, gastroesophageal reflux disease
*General disorders:* asthenia, fatigue, malaise, peripheral edema, pain, pyrexia
*Hepatobiliary disorders:* elevated transaminases, hepatomegaly
*Infections and infestations:* bacterial vaginosis, Candida infection, candiduria
*Metabolism and nutrition disorders:* polydipsia
*Musculoskeletal and connective tissue disorders:* arthralgia, back pain, myositis
*Nervous system disorders:* ageusia, dizziness, dysgeusia, dystonia, migraine, paresthesia, presyncope, somnolence, syncope
*Psychiatric disorders:* confusion
*Renal and urinary disorders:* urine odor abnormal
*Reproductive system and breast disorders:* perineal pain, vaginal discharge, vulvovaginal pruritus
*Respiratory disorders:* cough, dyspnea
*Skin and subcutaneous tissue disorders:* angioedema, pruritus, rash
*Vascular disorders:* flushing, hypertension

Adverse Reactions Occurring with Probenecid (a component of ORLYNVAH)
The following adverse reactions associated with the use of probenecid (a component of ORLYNVAH) were identified in clinical studies or postmarketing reports. Because some of these reactions were 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.

Adverse reactions not observed in clinical studies of ORLYNVAH that have been observed with probenecid (a component of ORLYNVAH) include:
*Gastrointestinal disorders*: hepatic necrosis, anorexia, sore gums
*Hematologic*: aplastic anemia, leukopenia, and hemolytic anemia which in some patients could be related to genetic deficiency of glucose-6-phosphate dehydrogenase in red blood cells, anemia
*Immune system disorders:* anaphylaxis, urticaria
*Metabolism and nutrition disorders:* precipitation of acute gouty arthritis
*Renal and urinary disorders:* nephrotic syndrome, uric acid stones with or without hematuria, renal colic, costovertebral pain, urinary frequency
*Skin and subcutaneous tissue disorders:* alopecia

# 7 DRUG INTERACTIONS

## 7.1 Potential for ORLYNVAH to Affect Other Drugs

Probenecid (a component of ORLYNVAH) is an inhibitor of organic anion transporters 1 and 3 (OAT1/3) and may increase plasma concentrations of drugs that are dependent on OAT1/3 for elimination. Table 2 provides a list of established or potentially clinically significant drug interactions.

**Table 2 Established and Other Potentially Clinically Significant Drug Interactions**

| Concomitant Drug/Drug Class | Effect on Drug Concentration | Recommendation |
|---|---|---|
| Ketorolac tromethamine | ↑ ketorolac tromethamine | Contraindicated |
| Ketoprofen | ↑ ketoprofen | Concomitant use is not recommended. |
| Indomethacin | ↑ indomethacin | May increase the risk of adverse reactions. Refer to drug-specific prescribing information for dosage adjustment instructions. |
| Naproxen | ↑ naproxen | May increase the risk of adverse reactions. Refer to drug-specific prescribing information for dosage adjustment instructions. |
| Methotrexate | ↑ methotrexate | If concomitant use cannot be avoided, monitor more frequently for adverse reactions associated with methotrexate as recommended in its prescribing information. |
| Rifampin | ↑ rifampin | Monitor more frequently for adverse reactions associated with rifampin as recommended in its prescribing information. |
| Lorazepam | ↑ lorazepam | Follow the recommended lorazepam dosage modifications outlined in its prescribing information. |
| Oral Sulfonylureas | ↑ antidiabetic | Monitor more frequently for hypoglycemia. Follow recommended sulfonylurea dosage modifications in its prescribing information. |

Valproic Acid
No valproic acid dosage adjustment is recommended when used concomitantly with ORLYNVAH. No clinically significant reduction in plasma valproic acid concentrations was observed following concomitant use with ORLYNVAH *[see Clinical Pharmacology (12.3)]*.

### 7.2 Potential for Other Drugs to Affect ORLYNVAH

Sulopenem is a substrate of OAT3; therefore, drugs that inhibit OAT3 may increase sulopenem plasma concentrations *[see Clinical Pharmacology (12.3)]*. If concomitant use with ORLYNVAH is necessary, monitor more frequently for adverse reactions associated with ORLYNVAH (e.g., diarrhea and nausea) *[see Adverse Reactions (6.1)]*.

### 7.3 Drug/Laboratory Interactions

Treatment with ORLYNVAH may interfere with copper sulfate urine glucose tests, resulting in false-positive readings for glycosuria. Suspected glycosuria should be confirmed by using a test specific for glucose.

Falsely high readings for theophylline have been reported in an *in vitro* study, using the Schack and Waxler technique, when therapeutic concentrations of theophylline and probenecid (a component of ORLYNVAH) were added to human plasma.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

*Sulopenem Etzadroxil*
There are no available data on sulopenem etzadroxil use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Sulopenem etzadroxil was orally administered during organogenesis in embryo-fetal studies in mice, rats, and rabbits. In pregnant mice, maternal toxicity and an increased litter incidence of a fetal malformation, cleft palate, was observed with an oral dose of sulopenem etzadroxil associated with plasma sulopenem exposure approximately 23 times the clinical sulopenem exposure for the maximum recommended human dose (MRHD) of 1000 mg/day sulopenem etzadroxil. In pregnant rats and rabbits, orally administered sulopenem etzadroxil was not associated with fetal malformations at any dose, but in rats, maternal toxicity and reduced fetal body weights occurred at sulopenem etzadroxil doses associated with sulopenem plasma exposures approximately 2 and 6 times, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil. In rabbits, maternal toxicity and reduced fetal body weights occurred at sulopenem etzadroxil doses associated with sulopenem plasma exposures approximately 0.1 and 0.2 times, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil.

*Probenecid*
Available published data over several decades of probenecid use in pregnant woman have not identified a drug-associated risk of miscarriage, major birth defects, or adverse maternal or fetal outcomes. Probenecid crosses the placental barrier and appears in cord blood.

The estimated 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.

Data

*Animal Data*

*Sulopenem etzadroxil:*
In an embryo-fetal development (EFD) study in mice, sulopenem etzadroxil was administered to pregnant females in oral doses of 100, 400, and 2000 mg/kg/day during the period of organogenesis from GD 6 to GD 15. Reduced fetal body weights and a fetal malformation, cleft palate, occurred with an increased fetal and litter incidence in the 2000 mg/kg/day group (approximately 23 times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison). At the same dose, maternal clinical signs (rales, dyspnea, decreased motor activity) were observed, and maternal body weight gains were reduced. No maternal toxicity or fetal malformations occurred with doses ≤ 400 mg/kg/day (approximately 3 times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison).

In an EFD study in rats, sulopenem etzadroxil was administered to pregnant females in oral doses of 100, 400, and 2000 mg/kg/day during the period of organogenesis from GD 6 to GD 17. Maternal body weights and food consumption were reduced in the 400 and 2000 mg/kg/day groups. No fetal malformations were observed at any sulopenem etzadroxil dose, but fetal body weights were reduced in the 2000 mg/kg/day group (approximately equal to 11 times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison). The doses at which no maternal toxicity or fetal toxicity occurred were, respectively, 100 mg/kg/day and 400 mg/kg/day (less than or equal to and approximately 2 times respectively the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison).

In an EFD study in rabbits, sulopenem etzadroxil was administered intravenously to pregnant females in doses of 5, 15, and 50 mg/kg/day during the period of organogenesis from GD 7 to GD 19. Maternal body weight gain and food consumption were decreased in all the sulopenem etzadroxil dose groups. No fetal malformations occurred, but the number of fetal resorptions and postimplantation loss were increased and the number of viable fetuses and fetal body weights were decreased in the 15 and 50 mg/kg/day groups (approximately 0.2-times and equal to, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison). The dose at which no fetal toxicity occurred was 5 mg/kg/day (approximately 0.1-times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison).

In a pre- postnatal study in rats, sulopenem etzadroxil was administered by oral gavage to pregnant females from GD 6 through the lactation period to Lactation Day (LD) 20 in maternal doses of 100, 300, and 1000 mg/kg/day.

No adverse effects on the survival, growth, behavior, or reproduction of first-generation offspring occurred with any of the sulopenem etzadroxil doses up to the high dose of 1000 mg/kg/day (approximately 10-times the MRHD of sulopenem etzadroxil based on body surface area comparison).

## 8.2 Lactation

Risk Summary

There are no data on the presence of sulopenem etzadroxil or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production. The active metabolite of sulopenem etzadroxil, sulopenem, was present in rat milk after oral dosing of sulopenem etzadroxil to lactating female rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Probenecid is present in human milk based on a case report. There are no reports of adverse effects in infants associated with probenecid exposure through breastmilk. There is no information on the effects of probenecid on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ORLYNVAH and any potential adverse effects on the breast-fed child from ORLYNVAH or from the underlying maternal condition.

## 8.4 Pediatric Use

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

Juvenile Animal Toxicity Data

In a toxicology study with juvenile rats, sulopenem etzadroxil was orally administered from postnatal day (PND) 5 to PND 90 (85 days of dosing) in doses of 25, 75, and 225 mg/kg/day. Juvenile rats exhibited kidney toxicity including tubular epithelial degeneration and tubule concretions at doses ≥ 25 mg/kg/day (approximately 0.3 times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison).

## 8.5 Geriatric Use

In uUTI Trial 1, there were 436 patients 65 years of age and older *[see Clinical Studies (14.1)]*. Of the total number of ORLYNVAH-treated patients in this study, 224 (20.2%) were 65 years of age and older, while 80 (7.2%) were 75 years of age and older. No overall differences in safety or effectiveness of ORLYNVAH were observed between patients 65 years and older and younger adult patients.

In uUTI Trial 2, there were 452 patients 65 years of age and older *[see Clinical Studies (14.1)]*. Of the total number of ORLYNVAH-treated patients in this study, 218 (26.2%) were 65 years of age and older, while 86 (10.3%) were 75 years of age and older. No overall differences in safety or effectiveness of ORLYNVAH were observed between patients 65 years and older and younger adult patients.

No clinically meaningful differences in the pharmacokinetics of ORLYNVAH were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3)]*.

No dosage adjustment based on age is required. ORLYNVAH is known to be substantially excreted by the kidney, and geriatric patients are anticipated to have reduced renal function. Recommendations for use in elderly patients should be based on renal function *[see Dosage and Administration (2.2), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

## 8.6 Renal Impairment

Increases in sulopenem plasma concentrations were observed with mild, moderate and severe renal impairment; however, the available safety information does not suggest a need for dosage adjustments in these patients *[see Clinical Pharmacology (12.3)]*. Administration of ORLYNVAH is not recommended in patients with CrCL less than 15 mL/min and patients on hemodialysis because the pharmacokinetics of sulopenem have not been studied in this population.

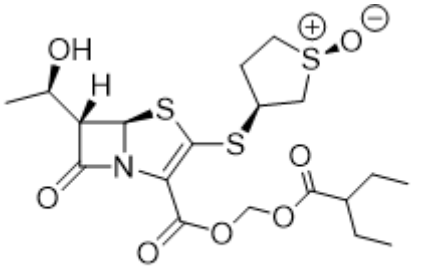
## 10 OVERDOSAGE

There is no information on clinical signs and symptoms associated with an overdose of ORLYNVAH. No clinical information is available on the use of hemodialysis to treat ORLYNVAH overdosage.

## 11 DESCRIPTION

ORLYNVAH (sulopenem etzadroxil and probenecid) tablets contain sulopenem etzadroxil, a penem antibacterial drug, and probenecid, a renal tubular transport inhibitor .

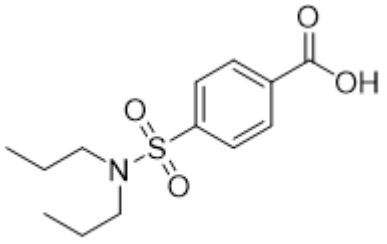
The chemical name of sulopenem etzadroxil is 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[[(1*R*,3*S*)- tetrahydro-1-oxido-3-thienyl]thio]-, (2-ethyl-1-oxobutoxy)methyl ester, (5*R*,6*S*)-. See Figure 1 for sulopenem etzadroxil chemical structure and chemical formula. The molecular weight of sulopenem etzadroxil is 477.61 g/mol.




Chemical Formula: $C_{19}H_{27}NO_7S_3$

**Figure 1. Sulopenem Etzadroxil Chemical Structure and Formula**

The chemical name for probenecid is 4-[(dipropylamino) sulfonyl] benzoic acid. See Figure 2 for probenecid chemical structure and chemical formula. The molecular weight of probenecid is 285.36 g/mol**.**




Chemical Formula: $C_{13}H_{19}NO_4S$

**Figure 2. Probenecid Chemical Structure and Formula**

ORLYNVAH are pink bilayer tablets for oral use containing 500 mg of sulopenem etzadroxil and 500 mg of probenecid and the following inactive ingredients: croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The film coating contains carmine, lecithin polyvinyl alcohol, talc, titanium dioxide, and xanthan gum.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

ORLYNVAH is a combination of sulopenem etzadroxil, a penem antibacterial drug *[see Microbiology 12.4]* and probenecid, a renal tubular inhibitor. Probenecid inhibits OAT3-mediated renal clearance of sulopenem, resulting in increased plasma concentrations of sulopenem.

## 12.2 Pharmacodynamics

Similar to other beta-lactam antimicrobial drugs, the percentage of time that unbound plasma concentrations of sulopenem exceed the sulopenem minimum inhibitory concentration (MIC) against the infecting organism has been shown to best correlate with efficacy in *in vitro* models of infection.

Cardiac Electrophysiology

At a concentration of 40 times or greater than that achieved after a single oral administration of ORLYNVAH, sulopenem does not prolong the QTc interval to a clinically relevant extent.

## 12.3 Pharmacokinetics

Sulopenem etzadroxil is a prodrug *[see Microbiology 12.4]*. The pharmacokinetics of sulopenem and probenecid were characterized in healthy subjects following single oral administration of ORLYNVAH (500 mg sulopenem etzadroxil and 500 mg probenecid). Pharmacokinetic parameters are presented in Table 3 as mean [coefficient of variation (%CV)] unless otherwise specified.

**Table 3. Pharmacokinetics of Sulopenem and Probenecid in Plasma after Single Oral Dose Administration of ORLYNVAH in Healthy Subjects**

| Parameter | | Sulopenem | | Probenecid | |
|---|---|---|---|---|---|
| | | Fasted | Fed[a] | Fasted | Fed[a] |
| **General Information** | | | | | |
| Exposure[b] | | | | | |
| | $C_{max}$ | 1.84 (39.1) | 2.66 (43.6) | 41.2 (38.2) | 30.4 (30.9) |
| | $AUC_{0\text{-}inf}$ | 4.85 (25.3) | 7.41 (22.7) | 255 (35.6) | 237 (35.2) |
| Dose Proportionality[b] | | Dose Proportional | | unknown | |
| Accumulation | | None | | unknown | |
| **Absorption** | | | | | |
| Bioavailability | | 40% | 64% | unknown | |
| $T_{max}$ Median (range) | | 1.0 (0.5 to 3.0) | 2.0 (1.0 -3.0) | 3.0 (1.0 – 10.0) | 2.0 (1.50 to 6.0) |
| *Effect of Food* | | | | | |
| High fat meal[a] (Fed:Fasted ratio) | $C_{max}$ | Increased 45% | | Decreased 27% | |
| | $AUC_{0\text{-}inf}$ | Increased 48% | | Decreased 8% | |
| **Distribution** | | | | | |
| Apparent Volume of Distribution (Liters) (mean (SD)) | | 134 (51.36) | 92.09 (33.43) | 8.81 (3.91) | 11.94 (3.46) |
| Protein Binding[c] | | 11% | | Unknown | |
| **Elimination** | | | | | |
| Half-Life (hours) (mean (SD)) | | 1.18 (0.24) | 1.28 (0.49) | 2.93 (0.83) | 3.83 (0.50) |
| Apparent Clearance (L/hour) (mean (SD)) | | 77.6 (19.77) | 50.55 (11.60) | 2.06 (0.70) | 2.22 (0.76) |
| *Metabolism* | | | | | |
| Primary Pathway | | Sulopenem etzadroxil is hydrolyzed by esterases to active sulopenem then further metabolized by hydrolysis followed by dehydrogenation | | unknown | |

| Major Metabolites | M1a and M1b[d] (inactive) | unknown |
|---|---|---|
| *Excretion*[e] | | |
| Feces | 44.3% (26.9% unchanged) | unknown |
| Urine | 40.8% (3.1% unchanged) | unknown |

*Abbreviations:* $C_{max}$ = maximum plasma concentration; AUC= area under the time concentration curve; $T_{max}$ = time to peak concentration

[a] A high fat meal is 800-1000 calories, approximately 50% of total calories from fat
[b] No clinically significant sulopenem divergence from dose-proportionally was observed over a dose range of 400 mg to 2000 mg (0.8 to 4 times the approved recommended sulopenem etzadroxil dosage)
[c]Independent of concentration over a range of 1 to 100 µg/mL
[d] Sulopenem, M1a and M1b, accounted for 32%, 21.8% and 43.6% of circulating radioactivity, respectively
[e]After a single oral dose of radiolabeled sulopenem etzadroxil 2000 mg healthy adult subjects

Specific Populations

No clinically significant differences in the pharmacokinetics of sulopenem were observed based on age, sex or weight. The effect of hepatic impairment on sulopenem pharmacokinetics is unknown.

*Patients with Renal Impairment*
Sulopenem mean plasma $AUC_{0\text{-}inf}$ increased by 2-fold in patients with mild (CrCL 60 to 89 mL/min), estimated by Cockcroft-Gault equation), by 3-fold in patients with moderate (CrCL 30 to 59 mL/min) and by 7.4-fold in patients with severe (CrCL15 to 29 mL/min) renal impairment following administration of 1000 mg oral sulopenem etzadroxil (not a recommended dosing regimen) *[see Dosage and Administration (2.1)]*. The effect of kidney failure (CrCL<15 mL/min) or hemodialysis on sulopenem pharmacokinetics is unknown.

Drug Interaction Studies

*Clinical Studies*
*Effect of Other Drugs on the Pharmacokinetics of ORLYNVAH:*

No clinically significant differences in the pharmacokinetics of sulopenem were observed when ORLYNVAH was administered concomitantly with oral itraconazole (P-gp inhibitor), pantoprazole (gastric-acid reducing agent) or aluminum hydroxide (gastric acid-reducing agent).

No clinically significant differences in the pharmacokinetics of valproic acid were observed when used concomitantly with ORLYNVAH. Although there are case reports in the published literature that suggest concomitant use of carbapenems result in a reduction in valproic acid concentrations, the probenecid component of ORLYNVAH appears to counteract any potential effect of sulopenem on valproic acid *[see Drug Interactions (7.1)]*.

*Effect of ORLYNVAH on the Pharmacokinetics of Other Drugs:*

Coadministration of multiple doses of 500 mg sulopenem etzadroxil with valproic acid decreased valproic acid plasma $AUC_{0\text{-}tau}$ and $C_{max}$ by approximately 25% and 19%, respectively. However, no clinically significant differences in the pharmacokinetics of valproic acid were observed when administered concomitantly with ORLYNVAH. $AUC_{0\text{-}tau}$ and $C_{max}$ decreased by 8.4% and 7%, respectively, with concomitant administration of ORLYNVAH.

*In Vitro Studies*
*CYP450 Enzymes:*

Sulopenem does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A or induce CYP1A2, CYP2B6, or CYP3A4/5.

*Transporter Systems:*

Sulopenem is a substrate of OAT3 and does not inhibit BCRP, P-gp, BSEP, MATE1, MATE2K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2. Probenecid is a substrate for BCRP and an inhibitor of OAT1/3, but does not inhibit BSEP, P-gp, or MRP2.

## 12.4 Microbiology

Mechanism of Action

Sulopenem etzadroxil is a prodrug that is hydrolyzed to the active drug sulopenem after oral administration. Sulopenem has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of sulopenem results from the inhibition of cell wall synthesis and is mediated through sulopenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, sulopenem demonstrated binding affinity for PBPs in the following order: PBP2 > PBP1A > PBP1B > PBP4 > PBP3 > PBP5/6.

Resistance

Resistance to sulopenem is caused by certain extended spectrum beta-lactamases (ESBLs) including carbapenemases, alteration of PBPs, over expression of efflux pumps and loss of outer membrane porins. Sulopenem demonstrated activity against Enterobacterales in the presence of certain beta-lactamases and ESBLs, e.g., AmpC, CTX-M, TEM, SHV. Sulopenem resistant mutants were selected in vitro at a frequency of $1\times10^{-8}$.

Interaction with Other Antimicrobials

*In vitro* studies with sulopenem did not demonstrate antagonism with any of the following antimicrobials: amoxicillin, aztreonam, ceftriaxone, doxycycline, gentamicin, levofloxacin, nitrofurantoin, vancomycin or trimethoprim-sulfamethoxazole. The clinical significance of these *in vitro* findings is unknown.

Antimicrobial Activity

Sulopenem has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1.1)]*:

Gram-negative bacteria
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

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 sulopenem against isolates of similar genus or organism group. However, the efficacy of sulopenem in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria
- *Staphylococcus saprophyticus*
- *Streptococcus agalactiae*

Gram-negative bacteria
- *Citrobacter freundii*
- *Citrobacter koseri*
- *Enterobacter cloacae* species Complex
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Proteus vulgaris*
- *Providencia alcalifaciens*
- *Providencia stuartii*

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, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies in animals have not been conducted with ORLYNVAH.

Mutagenesis

*Sulopenem Etzadroxil*

Sulopenem etzadroxil was negative for mutations in an in vitro Ames assay with and without metabolic activation but positive for chromosome aberrations with and without metabolic activation in vitro in peripheral human lymphocytes and Chinese hamster ovary cells. In vivo, sulopenem etzadroxil was negative for genetic toxicity in a bone marrow micronucleus assay in rats.

*Sulopenem*

Sulopenem did not induce mutations in a reverse mutation assay in bacterial cells with and without metabolic activation or in a CHO HGPRT mammalian cell mutation assay with and without metabolic activation. Sulopenem was positive for chromosome aberrations in vitro in V79 Chinese hamster lung cells, but negative for genetic toxicity in vivo in bone marrow micronucleus assays in mice and rats.

*Probenecid*

Probenecid was shown to be negative for mutagenicity in an in vitro Ames assay with and without metabolic activation and negative for chromosome aberrations in an in vitro chromosome aberration assay in Chinese hamster ovary cells with and without metabolic activation.

Impairment of Fertility

*Sulopenem etzadroxil*

Male and female fertility and early embryonic development were examined in rats (20/sex/group) orally administered sulopenem etzadroxil in daily doses of 100, 400, or 2000 mg/kg beginning 28 days prior to mating and throughout the mating period in males and for 14 days before mating, throughout the mating period, and until Gestation Day (GD) 7 in females. There were no treatment-related effects on estrous cycle length, mating and fertility rates, implantation, conceptus viability, sperm concentration and motility, or accessory male sex glands weights. No adverse effects on male and female fertility or early embryonic development in female rats were observed at doses up to 2000 mg/kg/day (approximately 10- and 12-times in male and female rats, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison).

*Probenecid*

No fertility studies have been conducted with probenecid.

### 13.2 Animal Toxicology and/or Pharmacology

In a toxicology study in monkeys, daily oral administration of sulopenem etzadroxil for 30 days was associated with reduced red blood cell counts and increased reticulocytes at doses of ≥ 400 mg/kg/day (approximately 6-times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on AUC comparison). In the same animals, positive Coomb's assay results demonstrated positive reactions for polyspecific anti-human globulin and anti-IgG suggesting red cell loss may have been mediated by antibodies. Similar findings were also observed in toxicology studies with sulopenem administered intravenously to monkeys.

## 14 CLINICAL STUDIES

### 14.1 Uncomplicated Urinary Tract Infections

Trial 1

A total of 2222 adult women with uncomplicated urinary tract infections (uUTI) were randomized and 2214 received trial medications in a randomized, double-blind clinical trial (Trial 1) (NCT05584657) comparing oral ORLYNVAH (sulopenem etzadroxil 500 mg and probenecid 500 mg) twice daily for 5 days to oral amoxicillin/clavulanate 875 mg/125 mg twice daily for 5 days.

The microbiological modified intent-to-treat (micro-MITT) population, which included all patients who had at least one uropathogen isolated at baseline ($\geq 10^5$ CFU/mL) and received at least one dose of study drug, consisted of 990 patients; the median age was 51 years and median weight was 73.5 kg. Patients were enrolled only from the United States. Patients were Caucasian (79.7%), African American (17.0%) or of another race (3.3%).

Composite response (combined microbiological response and clinical cure rates) was determined by comparing the response rate of ORLYNVAH to amoxicillin/clavulanate at the TOC visit (12 days after randomization) in the micro-MITT population as well as in two sub-populations: a) micro-MITTS (micro-MITT population with baseline pathogens susceptible to amoxicillin/clavulanate, MIC ≤8/4 μg/mL) and b) micro-MITTR (micro-MITT population with baseline pathogens non-susceptible to amoxicillin/clavulanate, MIC ≥16/8 μg/mL). Clinical cure was defined as the resolution of patient-reported uUTI symptoms and no new uUTI symptoms. Microbiological response was defined as a reduction of all baseline uropathogens to less than $10^3$ CFU/mL in the urine.

ORLYNVAH demonstrated efficacy in the micro-MITTS population. The micro-MITTR population was small (N=67) and had insufficient power to draw conclusions regarding efficacy (Table 4).

**Table 4. Composite Response[1] at the Test of Cure Visit in Patients with uUTI, Trial 1**

| Study Population | ORLYNVAH[a] n/N (%) | Amoxicillin/ clavulanate[b] n/N (%) | Treatment Difference (95% CI)[c] |
|---|---|---|---|
| **micro-MITTS[d] Population** | | | |
| Composite response | 296/480 (61.7) | 243/442 (55.0) | 6.7 (0.3, 13.0) |
| Clinical cure | 371/480 (77.3) | 339/442 (76.7) | 0.6 (-4.8, 6.1) |
| Microbiological response | 361/480 (75.2) | 295/442 (66.7) | 8.5 (2.6, 14.3) |
| **micro-MITTR[e] population** | | | |
| Composite response | 22/42 (52.4) | 17/25 (68.0) | -15.6 (-37.5, 9.1) |
| Clinical cure | 26/42 (61.9) | 18/25 (72.0) | -10.1 (-31.5, 14.0) |
| Microbiological response | 29/42 (69.0) | 20/25 (80.0) | -11.0 (-30.7, 12.0) |

[1]Combined Clinical and Microbiological Success; [a] 500 mg/500 mg orally twice daily for 5 days; [b] 875 mg/125 mg orally twice daily for 5 days; [c] The 95% confidence interval (CI) was calculated using the unstratified Miettinen and Nurminen method; [d] microbiological modified intent-to-treat population with baseline pathogens susceptible (MIC ≤8/4 μg/mL) to amoxicillin/clavulanate; [e] microbiological modified intent-to-treat population with baseline pathogens nonsusceptible (MIC ≥16/8 μg/mL) to amoxicillin/clavulanate.

Composite response rates by pathogen are presented in Table 5.

**Table 5. Composite Response Rate at Test of Cure by Baseline Pathogen from Patients with uUTI, Trial 1**

| Study Population | ORLYNVAH[a] n/N (%) | Amoxicillin/clavulanate[b] n/N (%) |
|---|---|---|
| **micro-MITTS Population** | | |
| *Escherichia coli* | 251/400 (62.8) | 210/374 (56.1) |
| *Klebsiella pneumoniae* | 31/57 (54.4) | 22/50 (44.0) |
| *Proteus mirabilis* | 5/13 (38.5) | 6/13 (46.2) |
| **micro-MITTR Population** | | |
| *Escherichia coli* | 12/23 (52.2) | 9/12 (75.0) |
| *Klebsiella pneumoniae* | 0 | 0 |
| *Proteus mirabilis* | 0 | 0 |

[a] 500 mg/500 mg orally twice daily for 5 days; [b] 875 mg /125 mg orally twice daily for 5 days

Trial 2

A total of 1660 adult women with uUTI were randomized and received trial medications in a multinational randomized, double-blind clinical trial (Trial 2) (NCT03354598) comparing oral ORLYNVAH (sulopenem etzadroxil 500 mg and probenecid 500 mg) twice daily for 5 days to oral ciprofloxacin 250 mg twice daily for 3 days. The micro-MITT population, which included all patients who had at least one uropathogen isolated at baseline ($\geq 10^5$ CFU/mL), consisted of 1105 patients; the median age was 53 years; median weight in the randomized population was 70.4 kg. Patients were enrolled from the United States (55%) and Eastern Europe (45%). Patients were Caucasian (90%), African American (9%) or of other races (1%).

Composite response (combined microbiological response and clinical cure) was determined by comparing the response rate of ORLYNVAH to ciprofloxacin at the TOC visit (12 days after randomization) in two primary populations:
a) micro-MITTS (micro-MITT population with baseline pathogens susceptible to ciprofloxacin, MIC ≤1 μg/mL) and b) micro-MITTR (micro-MITT population with baseline pathogens non-susceptible to ciprofloxacin, MIC ≥2 μg/mL). Clinical cure was defined as the resolution of patient-reported uUTI symptoms and no new uUTI symptoms. Microbiological response was defined as a reduction of all baseline uropathogens to less than $10^3$ CFU/mL in the urine.

ORLYNVAH demonstrated efficacy in the micro-MITTR population but did not demonstrate efficacy in the micro-MITTS population (Table 6).

**Table 6 Composite Response[1] at the Test of Cure Visit in Patients with uUTI, Trial 2**

| Study Population | ORLYNVAH[a] n/N (%) | Ciprofloxacin[b] n/N (%) | Treatment Difference (95% CI)[c] | P value[d] |
|---|---|---|---|---|
| **micro-MITTR[e] Population** | | | | |
| Composite response | 78/162 (48.1) | 49/149 (32.9) | 15.3 (4.3, 25.8) | 0.006 |
| Clinical cure | 136/162 (84.0) | 69/149 (46.3) | 19.5 (10.0, 29.0) | |
| Microbiological response | 92/162 (56.8) | 66/149 (44.3) | 12.5 (1.4, 23.3) | |
| **micro-MITTS[f] Population** | | | | |
| Composite response | 227/376 (60.4) | 300/418 (71.8) | -11.4 (-17.9, -4.8) | |
| Clinical cure | 205/376 (81.1) | 351/418 (84.0) | -2.9 (-8.2, 2.4) | |
| Microbiological response | 262/376 (69.7) | 336/418 (80.4) | -10.7 (-16.7, -4.7) | |

[1]Combined Clinical Cure and Microbiological Response; [a] 500 mg/500 mg orally twice daily for 5 days; [b] 250 mg PO twice daily for 3 days; [c] The 95% confidence interval (CI) was calculated using the unstratified Miettinen and Nurminen method; [d] The P value was calculated using Cochran– Mantel–Haenszel test; [e]microbiological modified intent-to-treat population with baseline pathogens susceptible (MIC ≤1 μg/mL) to ciprofloxacin; [f]microbiological modified intent-to-treat population with baseline pathogens nonsusceptible (MIC ≥2 μg/mL) to ciprofloxacin

Composite response rates by pathogen are presented in Table 7.

**Table 7 Composite Response Rate at Test of Cure by Baseline Pathogen from uUTI Trial 2**

| | ORLYNVAH[a] n/N (%) | Ciprofloxacin[b] n/N (%) |
|---|---|---|
| **micro-MITTR Population** | | |
| *Escherichia coli* | 63/141 (44.7) | 41/131 (31.3) |
| *Klebsiella pneumoniae* | 9/15 (60.0) | 7/14 (50.0) |
| *Proteus mirabilis* | 8/9 (88.9) | 3/6 (50.0) |
| **micro-MITTS Population** | | |
| *Escherichia coli* | 187/316 (59.2) | 244/348 (70.1) |
| *Klebsiella pneumoniae* | 23/37 (62.2) | 24/35 (68.6) |
| *Proteus mirabilis* | 5/9 (55.6) | 10/11 (90.9) |

[a] 500 mg/500 mg orally twice daily for 5 days; [b] 250 mg PO twice daily for 3 days

## 14.2 Complicated Urinary Tract Infections - Lack of Efficacy

ORLYNVAH is not indicated for the treatment of complicated urinary tract infections. Trial 3 (NCT03357614) was a phase 3, multi-center, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem etzadroxil and probenecid with that of IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate for the treatment of complicated urinary tract infections (cUTI). Trial 3 did not demonstrate the efficacy of sulopenem IV followed by oral sulopenem etzadroxil and probenecid for the primary endpoint of composite response (combined clinical and microbiologic response) in the microbiologic modified intent-to-treat (micro-MITT) population at the test-of-cure visit on Day 21 *[see Indications and Usage (1.1)]*.

### 14.3 Complicated Intra-abdominal Infections - Lack of Efficacy

ORLYNVAH is not indicated for the treatment of complicated intra-abdominal infections. Trial 4 (NCT03358576) was a phase 3, multi-center, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem etzadroxil and probenecid with that of IV ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin/clavulanate for the treatment of complicated intra-abdominal infections (cIAI). Trial 4 did not demonstrate the efficacy of IV sulopenem followed by oral sulopenem etzadroxil and probenecid for the primary endpoint of clinical response in the micro-MITT at the test-of-cure visit on Day 28 *[see Indications and Usage (1.1)]*.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

ORLYNVAH tablets are supplied as pink, oval-shaped, film-coated, fixed-dose, bilayer combination tablets debossed with SULO on one side and plain on the other side, containing 500 mg of sulopenem etzadroxil and 500 mg of probenecid.

They are supplied as follows:

Bottles of 10 tablets with child-resistant caps (NDC pending)
Bottles of 30 tablets with child-resistant caps (NDC pending)

### 16.2 Storage and Handling

Store ORLYNVAH tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room temperature].

## 17 PATIENT COUNSELING INFORMATION

Allergic Reactions

Advise patients that allergic reactions, including serious allergic reactions, could occur, and that serious allergic reactions require immediate treatment. Patients should inform their healthcare provider about any previous hypersensitivity reactions to ORLYNVAH, other beta-lactam antibacterial drugs or probenecid *[see Warnings and Precautions (5.1)]*.

Diarrhea

Advise patients that diarrhea is a common problem caused by antibacterial drugs, including ORLYNVAH, and usually resolves when the drug is discontinued. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, patients should contact their healthcare provider *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Antibacterial Resistance

Patients should be counseled that ORLYNVAH should only be used to treat proven or strongly suspected susceptible uUTI. Antibacterial drugs do not treat viral infections (e.g., the common cold). When ORLYNVAH is

prescribed to treat proven or strongly suspected susceptible uUTI, patients should be told that although it is common to feel better early in the course of therapy, ORLYNVAH 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 ORLYNVAH or other antibacterial drugs in the future *[see Warnings and Precautions (5.5)]*.

Ketoprofen

Advise patients that concomitant use of ketoprofen with ORLYNVAH is not recommended *[see Drug Interactions (7.1)]*.

Manufactured for: Iterum Therapeutics U.S. Limited, Chicago, IL 60606 US

Patent Numbers: Available online at https://www.iterumtx.com/

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