New Drug Overview

Orlynvah (sulopenem etzadroxil and probenecid)

PDL Category: Urological Agents

Introduction

Disease Background:

- Urinary tract infections (UTI) can include cystitis and pyelonephritis (infection of the kidney/upper urinary tract) (*Gupta 2026*).
  - An uncomplicated urinary tract infection (uUTI) is an infection of the bladder (cystitis, lower urinary tract) in females who are not pregnant and who do not have functional or anatomical abnormalities in the urinary tract or other comorbidities that may lead to a more challenging infection to treat (*Gupta 2026, Orrange et al 2025*).
  - Pyelonephritis is generally characterized as a complicated UTI (cUTI) in clinical practice; however, its category may vary dependent on the professional organization (*Orrange et al 2025*).
- uUTIs and cUTIs are included as the most common infections in outpatients overall (*Orrange et al 2025*).
  - UTIs are more common in women than men.
    - Data suggests about 50-60% of women develop a UTI at some point during their life, although prevalence differs by age.
- The common symptoms of cystitis include dysuria, urinary frequency, urinary urgency, and suprapubic pain. In addition, although not as common, gross hematuria may occur (*Orrange et al 2025*).
- Empiric antibiotic treatment is suitable when there is a robust instinct that a nonpregnant female has acute uUTI (*Orrange et al 2025*).
  - Nitrofurantoin is generally listed as a first-line treatment, along with fosfomycin or pivmecillinam.
- Orlynvah was FDA approved in 2024.

Pharmacology/Usage

- Orlynvah (sulopenem etzadroxil and probenecid) is a combination of sulopenem etzadroxil (a penem antibacterial drug) and probenecid (a renal tubular transport inhibitor).
  - Probenecid inhibits OAT3-mediated renal clearance of sulopenem, resulting in increased plasma concentrations of sulopenem.
  - Sulopenem etzadroxil is a prodrug that is hydrolyzed to the active drug sulopenem after oral administration. It 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).

Indications

Table 1. Food and Drug Administration Approved Indications

Indication	Orlynvah (sulopenem etzadroxil & probenecid)
• 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. [a, b]	✔

[a] Limitations of use include that Orlynvah is not indicated for the treatment of complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI and not indicated for complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI.

[b] 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.

(Prescribing information: Orlynvah 2025)

- Information on indications, mechanism of action, pharmacokinetics, dosing, safety, and clinical efficacy summary has been obtained from the prescribing information for the individual products, except where noted otherwise.

Dosing and administration

Table 2. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Orlynvah (sulopenem etzadroxil & probenecid)	Film-Coated Tablets	Oral	BID X5 days with food.	• Use is not recommended in patients with creatinine clearance (CrCL) less than 15ml/min or patients on hemodialysis. • If a dose is missed, take the dose as soon as possible. Do not double the dose to make up for the missed dose.

See the current prescribing information for full details.

Clinical Efficacy Summary

- *Trial 1* assessed the efficacy of Orlynvah in a randomized, double-blind clinical trial that compared Orlynvah (sulopenem etzadroxil 500mg and probenecid 500mg) BID for 5 days to amoxicillin/clavulanate 875mg/125mg BID for 5 days.
  - This study included adult women (N=2,222) with uUTI.
  - The microbiological modified intent-to-treat (micro-MITT) population, which included all patients who had at least one uropathogen isolated at baseline and received at least one dose of study drug, included patients (N=990) with a median age of 51 years and median weight of 73.5kg. In addition, 79.7% were Caucasian.
  - Patients were enrolled only from the United States.
- The composite response (combined microbiological response and clinical cure rates) was determined by comparing the response rate of Orlynvah to amoxicillin/clavulanate at the test of cure (TOC) visit (12 days after randomization) in the micro-MITT population as well as in two sub-populations including
  - micro-MITTS (micro-MITT population with baseline pathogens susceptible to amoxicillin/clavulanate)
  - micro-MITTR (micro-MITT population with baseline pathogens non-susceptible to amoxicillin/clavulanate).
- 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 colony forming units/mL (CFU/mL) in the urine.
- Results demonstrated that 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.
  - Results are presented in the table below, which was adapted from the prescribing information.

Table 3. Efficacy results

Study population	Orlynvah n/N (%)	Amoxicillin/clavulanate n/N (%)	Treatment difference
micro-MITTS Population			
Composite response	296/480 (61.7%)	243/442 (55%)	6.7
Clinical Cure	371/480 (77.3%)	339/442 (76.7%)	0.6
Microbiological Response	361/480 (75.2%)	295/442 (66.7%)	8.5
micro-MITTR population			
Composite response	22/42 (52.4%)	17/25 (68%)	-15.6
Clinical Cure	26/42 (61.9%)	18/25 (72%)	-10.1
Microbiological Response	29/42 (69%)	20/25 (80%)	-11.0

- Composite response rates by pathogen are presented in the table below, which was adapted from the prescribing information.

Table 4. Composite Response Rate at TOC by baseline pathogen from patients with uUTI

Study population	Orlynvah n/N (%)	Amoxicillin/clavulanate n/N (%)
micro-MITTS Population		
Escherichia coli	251/400 (62.8%)	210/374 (56.1%)
Klebsiella pneumoniae	31/57 (54.4%)	22/50 (44%)
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

- *Trial 2* assessed the efficacy of Orlynvah in a multinational, randomized, double-blind clinical trial that compared Orlynvah (sulopenem etzadroxil 500mg and probenecid 500mg) BID for 5 days to ciprofloxacin 250mg BID for 3 days.
  - This study included adult women (N=1,660) with uUTI.
  - The micro-MITT population, which included all patients who had at least one uropathogen isolated at baseline consisted of patients (N=1,105) with a median age of 53 years and median weight in the randomized population of 70.4kg. In addition, 90% were Caucasian.

- Patients were enrolled from the United States (55%) and Eastern Europe (45%).

- The 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, including:
  - micro-MITTS (micro-MITT population with baseline pathogens susceptible to ciprofloxacin).
  - micro-MITTR (micro-MITT population with baseline pathogens non-susceptible to ciprofloxacin).
- 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.
  - Results are presented in the table below, which was adapted from the prescribing information.

Table 5. Efficacy results

Study population	Orlynvah n/N (%)	Ciprofloxacin n/N (%)	Treatment difference	p-value
micro-MITTR Population				
Composite response	78/162 (48.1%)	49/149 (32.9%)	15.3	0.006
Clinical Cure	136/162 (84.0%)	96/149 (64.4%)	19.5	
Microbiological Response	92/162 (56.8%)	66/149 (44.3%)	12.5	
micro-MITTS population				
Composite response	227/376 (60.4%)	300/418 (71.8%)	-11.4	
Clinical Cure	305/376 (81.1%)	351/418 (84.0%)	-2.9	
Microbiological Response	262/376 (69.7%)	336/418 (80.4%)	-10.7	

- Composite response rates by pathogen are presented in the table below, which was adapted from the prescribing information.

Table 6. Composite Response Rate at TOC by baseline pathogen from patients with uUTI

Study population	Orlynvah n/N (%)	Ciprofloxacin 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%)

Study population	Orlynvah n/N (%)	Ciprofloxacin n/N (%)
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%)

- Orlynvah is not indicated for the treatment of complicated urinary tract infections (cUTI).
  - Trial 3 was a phase 3, multicenter, 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 cUTI.
    - This trial did not demonstrate the efficacy of sulopenem IV followed by oral sulopenem etzadroxil and probenecid for the primary endpoint of composite response in the micro-MITT population at the TOC visit on day 21.
- Orlynvah is not indicated for the treatment of complicated intra-abdominal infections (cIAI).
  - Trial 4 was a phase 3, multicenter, 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 cIAI.
    - This trial 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 TOC visit on day 28.

Clinical guidelines

- There are currently no published guidelines addressing the use of Orlynvah for the treatment of uUTI, as the guidelines were published prior to FDA approval.
- Infectious Diseases Society of America (IDSA) notes that updated uUTI guidelines are in development. It is unknown whether Orlynvah will be included in these guidelines (*IDSA website*).
- **IDSA 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections** (*Tamma et al 2024*)
  - Preferred antibiotics for the treatment of uncomplicated cystitis caused by extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) include nitrofurantoin and trimethoprim-sulfamethoxazole (TMP/SMX).
  - Alternatives include ciprofloxacin, levofloxacin, and carbapenems; although effective, use is discouraged when nitrofurantoin or TMP/SMX are active.
  - An aminoglycoside (as a single dose) and oral fosfomycin (for *E. coli* only) are also alternative treatments for uUTI caused by ESBL-E.
- **IDSA and the European Society for Microbiology and Infectious Diseases (ESMID), 2010 update: International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women** (*Gupta et al 2011*).
  - These guidelines are limited to the treatment of UTI in premenopausal, nonpregnant women with no known urological abnormalities or comorbidities.
  - In women with acute uncomplicated cystitis (eg, absence of fever, flank pain, or other suspicion for pyelonephritis), antimicrobials should be considered based on (1) availability, (2) allergy history, and (3) tolerance.
  - Guideline-recommended first-line antibiotics include nitrofurantoin, TMP/SMX DS, fosfomycin, and pivmecillinam.

Safety summary

- **Contraindications:**
  - In patients with:
    - A history of hypersensitivity to the components of the product or other beta-lactam antibacterial drugs.
    - Known uric acid kidney stones.
  - Concomitant use of Orlynvah and ketorolac tromethamine.

- **Box Warning:** None.

- **Warnings and precautions:**
  - Hypersensitivity reactions, specifically cases of angioedema, have been reported in patients treated with Orlynvah. Serious and occasionally fatal hypersensitivity reactions, including anaphylaxis, and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. Before Orlynvah therapy is started, carefully inquire about previous hypersensitivity reactions to other carbapenems, cephalosporins, penicillin, or other beta-lactams because cross hypersensitivity among beta-lactam antibacterial drugs has been reported. In addition, severe allergic reactions and anaphylaxis have been reported with the use of probenecid. If an allergic reaction to Orlynvah occurs, discontinue the drug and start appropriate supportive measures.
  - *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.
    - 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 started as clinically indicated.
  - When prescribing Orlynvah to patients with a history of gout, appropriate measures to reduce the risk of uric acid kidney stone development should be started, such as increased fluid intake and alkalization of the urine. Note that Orlynvah is contraindicated in patients with known uric acid kidney stones.
  - Orlynvah may cause exacerbation of gout. When prescribing Orlynvah to patients with a known history of gout, ensure appropriate therapy of gout is instituted.
  - The probenecid component of Orlynvah may increase the risk of uric acid nephropathy in patients at risk for tumor lysis syndrome (TLS). When prescribing Orlynvah to patients with risk factors for TLS, take appropriate measures to reduce the risk.
  - 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.

- **Common adverse drug reactions**:
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Orlynvah) minus reported % incidence for amoxicillin/clavulanate. Please note that an incidence of 0% means the incidence was the same as or less than comparator.
    - The most frequently reported adverse events included diarrhea (6%), nausea (1%), vulvovaginal mycotic infection (1%), headache (0%), vomiting (1.6%), and abdominal pain (0).
  - Listed % incidence for adverse drug reactions= reported % incidence for drug (Orlynvah) minus reported % incidence for ciprofloxacin. Please note that an incidence of 0% means the incidence was the same as or less than comparator.

- The most frequently reported adverse events included diarrhea (7%), nausea (0%), vulvovaginal mycotic infection (1%), headache (0%), vomiting (1%), and abdominal pain (0%).

- **Drug interactions:**
  - The concomitant use of ketorolac tromethamine with Orlynvah is contraindicated.
  - The concomitant use of ketoprofen with Orlynvah is not recommended.
  - The concomitant of indomethacin or naproxen with Orlynvah may increase the risk of adverse reactions. Refer to the drug-specific prescribing information for dosage adjustment instructions.
  - If concomitant use of methotrexate and Orlynvah cannot be avoided, monitor more frequently for adverse reactions associated with methotrexate as recommended in its prescribing information.
  - With concomitant use of rifampin and Orlynvah, monitor more frequently for adverse reactions associated with rifampin as recommended in its prescribing information.
  - With concomitant use of lorazepam and Orlynvah, follow the recommended lorazepam dosage modifications outlined in its prescribing information.
  - With concomitant use of oral sulfonylureas and Orlynvah, monitor more frequently for hypoglycemia. Follow recommended sulfonylurea dosage modifications in its prescribing information.
  - Sulopenem is a substrate of OAT3; thus, drugs that inhibit OAT3 may increase sulopenem plasma concentrations. If concomitant use with Orlynvah is needed, monitor more frequently for adverse reactions associated with Orlynvah (eg, diarrhea and nausea).

- **Special populations:**
  - There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on sulopenem etzadroxil use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data of probenecid use in pregnant women have not identified a drug-associated risk of miscarriage, major birth defects, or adverse maternal or fetal outcomes.
  - The safety and efficacy of use in the pediatric population have not been established.

Conclusion

- An uncomplicated urinary tract infection (uUTI) is an infection of the bladder (cystitis, lower urinary tract) in females who are not pregnant and who do not have functional or anatomical abnormalities in the urinary tract or other comorbidities that may lead to a more challenging infection to treat (*Gupta 2026, Orrange et al 2025*).
- 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 include that Orlynvah is not indicated for the treatment of:
    - Complicated urinary tract infections (cUTI) or as step-down treatment after IV antibacterial treatment of cUTI.
    - Complicated intra-abdominal infections (cIAI) or as step-down treatment after IV antibacterial treatment of cIAI.
  - 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.
- Its safety and efficacy were assessed in two randomized, double-blind, active-controlled trials for uUTI treatment in adult women. One trial compared Orlynvah with amoxicillin/clavulanate and one trial compared Orlynvah with ciprofloxacin 250mg. Composite response was assessed in both studies.

- In Trial 1, Orlynvah demonstrated efficacy in the micro-MITTS population as compared with amoxicillin/clavulanate. However, the micro-MITTR population was small and had insufficient power to draw conclusions regarding efficacy.
- In Trial 2, Orlynvah demonstrated efficacy in the micro-MITTR population (p=0.006) as compared with ciprofloxacin but did not demonstrate efficacy in the micro-MITTS population.

- Current guidelines for uUTI do not include Orlynvah, as they were published prior to Orlynvah being FDA approved.

- There is no evidence to suggest that Orlynvah is safer or more effective than other currently preferred, more cost-effective medications. It is therefore recommended that Orlynvah remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

- **PDL Placement:**
  - ☐ Preferred
  - ☒ Non-Preferred

References

- Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Disease. *Clin Infect Dis*. 2011:52:e103-e120. doi: 10.1093/cid/ciq257
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