HIGHLIGHTS OF PRESCRIBING INFORMATION

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

TYZAVAN (vancomycin injection), for intravenous use
Initial U.S. Approval: 1958

----------RECENT MAJOR CHANGES----------

Boxed Warning	Removed	6/2025
Indications and Usage (1.1-1.5)		6/2025
Dosage and Administration (2.1, 2.3)		6/2025
Warnings and Precautions (5.1, 5.2)		6/2025

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

TYZAVAN is a glycopeptide antibacterial indicated for the treatment of the following infections in adult and pediatric patients (1 month and older) for whom appropriate dosing with this formulation can be achieved:

- Septicemia (1.1)
- Infective Endocarditis (1.2)
- Skin and Skin Structure Infections (1.3)
- Bone Infections (1.4)
- Lower Respiratory Tract Infections (1.5)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TYZAVAN and other antibacterial drugs, TYZAVAN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.6)

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

- If a dose of TYZAVAN is required that does not equal 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g, this product is not recommended for use and an alternative formulation of vancomycin should be considered. (2.1).
- For intravenous use only. Do **not** administer orally.
- Administer TYZAVAN by intravenous infusion over 60 minutes or greater to reduce the risk of infusion reactions (2.1)
- Recommended Dosage in Adult Patients with Normal Renal Function: 2 g divided either as 0.5 grams (g) every 6 hours or 1 g every 12 hours (2.2)
- Recommended Dosage in Pediatric Patients (1 Month and Older) with Normal Renal Function: 10 mg/kg per dose given every 6 hours (2.3)
- Recommended Dosage in Patients with Renal Impairment: See full prescribing information for recommended doses in patients with renal impairment (2.4)
- See full prescribing information for further important preparation and administration instructions (2.1, 2.5)

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

Injection: TYZAVAN contains 500 mg vancomycin in 100 mL, 750 mg vancomycin in 150 mL, 1 g vancomycin in 200 mL, 1.25 g vancomycin in 250 mL, 1.5 g vancomycin in 300 mL, 1.75 g vancomycin in 350 mL and 2 g vancomycin in 400 mL (5 mg/mL) of Water for Injection in single-dose flexible bags. (3)

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

Hypersensitivity to vancomycin (4)

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

- Infusion Reactions: Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain and "vancomycin infusion reactions"-which manifests as pruritus and erythema that involves the face, neck and upper body may occur with rapid intravenous administration. To reduce the risk of infusion reactions, administer TYZAVAN over a period of 60 minutes or greater and also prior to intravenous anesthetic agents. (2.1, 5.1)
- Nephrotoxicity: Monitor renal function in all patients receiving TYZAVAN. (5.2)
- Ototoxicity: Serial tests of auditory function may be helpful. (5.3)
- Severe Dermatologic Reactions: Discontinue TYZAVAN at the first appearance of signs and symptoms of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and linear IgA bullous dermatosis (LABD). (5.4)
- *Clostridioides difficile*-Associated Diarrhea (CDAD): Evaluate patients if diarrhea occurs. (5.5).
- Neutropenia: Periodically monitor leukocyte count. (5.7)
- Phlebitis and Other Administration Site Reactions: Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions are anaphylaxis, "vancomycin infusion reactions", acute kidney injury, hearing loss, neutropenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Anesthetic Agents: Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing. (2.1, 7.1)
- Piperacillin/Tazobactam: Increased incidence of acute kidney injury in patients receiving concomitant piperacillin/tazobactam and vancomycin as compared to vancomycin alone. Monitor kidney function in patients. (7.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2025

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 Septicemia

TYZAVAN is indicated in adults and pediatric patients (1 month and older) for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2) and Use in Specific Populations (8.4)]* for the treatment of septicemia due to:

- Susceptible isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.2 Infective Endocarditis

TYZAVAN is indicated in adults and pediatric patients (1 month and older) for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2) and Use in Specific Populations (8.4)]* for the treatment of infective endocarditis due to:

- Susceptible isolates of MRSA.
- Viridans group streptococci *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), *Enterococcus* species and *Corynebacterium* species. For enterococcal endocarditis, use TYZAVAN in combination with an aminoglycoside.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

TYZAVAN is indicated in adults and pediatric patients (1 month and older) for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2) and Use in Specific Populations (8.4)]* for the treatment of early-onset prosthetic valve endocarditis caused by *Staphylococcus epidermidis* in combination with rifampin and an aminoglycoside.

1.3 Skin and Skin Structure Infections

TYZAVAN is indicated in adults and pediatric patients (1 month and older) for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2) and Use in Specific Populations (8.4)]* for the treatment of skin and skin structure infections due to:

- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.4 Bone Infections

TYZAVAN is indicated in adults and pediatric patients (1 month and older) for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2) and Use in Specific Populations (8.4)]* for the treatment of bone infections due to:

- Susceptible isolates of MRSA and coagulase negative staphylococci.
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.5 Lower Respiratory Tract Infections

TYZAVAN is indicated in adults and pediatric patients (1 month and older) for whom appropriate dosing with this formulation can be achieved *[see Dosage and Administration (2) and Use in Specific Populations (8.4)]* for the treatment of lower respiratory tract infections due to:

- Susceptible isolates of MRSA
- Methicillin-susceptible staphylococci in penicillin-allergic patients, or those patients who cannot receive or who have failed to respond to other drugs, including penicillins or cephalosporins.

1.6 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness TYZAVAN and other antibacterial drugs, TYZAVAN 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 Important Administration Instructions

- If a dose of TYZAVAN is required that does not equal 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g, this product is not recommended for use and an alternative formulation of vancomycin should be considered.
- TYZAVAN is intended for intravenous use only.
- TYZAVAN is **not** to be administered orally.
- To reduce the risk of infusion related adverse reactions, administer TYZAVAN by intravenous infusion over 60 minutes or greater *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*. An infusion rate of 10 mg/min or less is associated with fewer infusion-related adverse reactions *[see Warnings and Precautions (5.1)]*. Infusion related adverse reactions may occur, however, at any rate or concentration.
- Drug additives should not be made to this solution.
- TYZAVAN concentrations of no more than 5 mg/mL are recommended in adults and pediatric patients *[see Dosage and Administration (2.2)]*. See also age-specific recommendations *[see Dosage and Administration (2.3)]*.
- Administer TYZAVAN prior to intravenous anesthetic agents to reduce the risk of infusion related adverse reactions *[see Warnings and Precautions (5.1)]*.
- Administer TYZAVAN by a secure intravenous route of administration to reduce the risk of local irritation and phlebitis reactions *[see Warnings and Precautions (5.8)]*.

2.2 Recommended Dosage in Adult Patients with Normal Renal Function

The usual daily intravenous dosage of TYZAVAN is 2 grams (g) divided either as 500 mg every 6 hours or 1 g every 12 hours. Administer each dose by intravenous infusion over a period of 60 minutes or greater. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose. The initial daily dose should be no less than 15 mg/kg.

2.3 Recommended Dosage in Pediatric Patients (1 Month and Older) with Normal Renal Function

If a dose of TYZAVAN is required that does not equal 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g, this product is not recommended for use and an alternative formulation of vancomycin should be considered *[see Use in Specific Populations (8.4)]*.

Pediatric Patients (Aged 1 Month and Older)

The usual intravenous dosage of TYZAVAN is 10 mg/kg per dose given every 6 hours. Each dose should be administered over a period of at least 60 minutes. Close monitoring of serum concentrations of vancomycin may be warranted in these patients.

2.4 Recommended Dosage in Adult Patients with Renal Impairment

Dosage adjustment must be made in adult patients with renal impairment. The initial dose of TYZAVAN should be no less than 15 mg/kg in patients with any degree of renal impairment.

In the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measure trough vancomycin serum concentrations to guide therapy, especially in seriously ill patients with changing renal function.

For functionally anephric patients, an initial dose of 15 mg/kg of body weight should be given to achieve prompt therapeutic serum concentration. A dose of 1.9 mg/kg/24 h should be given after the initial dose of 15 mg/kg.

2.5 Administration and Preparation and Storage Instructions for TYZAVAN

Administration Instructions

TYZAVAN in transparent single-dose flexible bag is for intravenous administration only.

TYZAVAN is a room temperature stable, ready-to-use drug product.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Preparation for Intravenous Administration and Storage Instructions:

1. Remove the flexible bag from aluminum overpouch.
2. Check for minute leaks by squeezing the bag firmly. If leaks are detected, discard solution because sterility may be impaired. Leaks may be more readily detected by wrapping the bag with blotting paper or a tissue before squeezing.
3. Do not add supplemental medication.
4. Visually inspect the flexible bag. If the outlet port protector is damaged, detached, or not present, discard the flexible bag as solution path sterility may be impaired. If after visual inspection the solution is cloudy or if an insoluble precipitate is noted or if any seals are not intact, the flexible bag should be discarded.
5. The solution in the flexible bag remains chemically stable for 28 days at room temperature (15°C - 25°C (59°F – 77ºF)) after removal from the aluminum overpouch. Discard unused drug.
6. Suspend the flexible bag from eyelet support.
7. Remove protector from outlet port at bottom of flexible bag.
8. Attach administration set. Refer to complete directions accompanying set.
9. Use sterile equipment.

Do **not** use flexible bags in series connections. Such use could result in an embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

2.6 Incompatibilities for Intravenous Use

Vancomycin solution has a low pH and may cause chemical or physical instability when it is mixed with other compounds.

Mixtures of solutions of vancomycin and beta-lactam antibacterial drugs have been shown to be physically incompatible. The likelihood of precipitation increases with higher concentrations of vancomycin. It is recommended to adequately flush the intravenous lines between the administration of these antibacterial drugs.

3 DOSAGE FORMS AND STRENGTHS

Injection: TYZAVAN(Vancomycin Injection, USP) is a ready to use clear, colorless to light brown sterile solution in single-dose flexible bags in the following strengths: 500 mg vancomycin in 100 mL (5 mg/mL), 750 mg vancomycin in 150 mL (5 mg/mL), 1 g vancomycin in 200 mL (5 mg/mL), 1.25 g vancomycin in 250 mL (5 mg/mL), 1.5 g vancomycin in 300 mL (5 mg/mL), 1.75 g vancomycin in 350 mL (5 mg/mL) and 2 g vancomycin in 400 mL (5mg/mL) of Water for Injection *[see Description (11)]*.

4 CONTRAINDICATIONS

TYZAVAN is contraindicated in patients with known hypersensitivity to vancomycin.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Hypotension, including shock and cardiac arrest, wheezing, dyspnea, urticaria, muscular and chest pain may occur with rapid TYZAVAN administration (e.g., over several minutes). The reactions may be more severe in pediatric patients *[see Use in Specific Populations (8.4)]*.

Rapid intravenous administration of TYZAVAN may also be associated with "vancomycin infusion reactions" which manifests as pruritus and erythema that involves the face, neck and upper body or pain and muscle spasm of the chest and back.

There have been reports that the frequency of infusion-related reactions (including hypotension, flushing, erythema, urticaria, and pruritus) increases with the concomitant administration of anesthetic agents.

Infusion-related adverse reactions are related to both the concentration and the rate of administration of TYZAVAN. Infusion-related adverse reactions may occur, however, at any rate or concentration. Administer TYZAVAN over a period of 60 minutes or greater to reduce the risk of infusion-related adverse reactions. In selected patients in need of fluid restriction, a concentration up to 10 mg/mL may be used; use of such higher concentrations may increase the risk of infusion-related adverse reactions. Administer TYZAVAN as a 60-minute infusion prior to administration of intravenous anesthetic agents when feasible to minimize infusion-related adverse reactions. Stop the infusion if a reaction occurs because this usually results in prompt cessation of these reactions.

5.2 Nephrotoxicity

TYZAVAN can result in acute kidney injury (AKI), including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. AKI is manifested by increasing blood urea nitrogen (BUN) and serum creatinine (Cr). The risk of AKI increases with higher vancomycin serum levels, prolonged exposure, concomitant administration of other nephrotoxic drugs,

concomitant administration of piperacillin-tazobactam *[see Drug Interactions (7.2)]*, volume depletion, pre-existing renal impairment and in critically ill patients and patients with co-morbid conditions that predispose to renal impairment.
Monitor serum vancomycin concentrations and renal function in all patients receiving TYZAVAN. More frequent monitoring is recommended in patients with comorbidities that predispose to impairment in renal function or are concomitantly receiving other nephrotoxic drugs, in critically ill patients, in patients with changing renal function, and in patients requiring higher therapeutic vancomycin levels. If acute kidney injury occurs, discontinue TYZAVAN or reduce the dose.

5.3 Ototoxicity

Ototoxicity has occurred in patients receiving vancomycin. It may be reversible or permanent. Ototoxicity manifests as tinnitus, hearing loss, dizziness or vertigo. The risk is higher in older patients, patients who are receiving higher doses, who have an underlying hearing loss, who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside or who have underlying renal impairment. Monitor for signs and symptoms of ototoxicity during therapy. Monitor serum vancomycin concentrations and renal function in all patients receiving parenteral vancomycin. Discontinue TYZAVAN if ototoxicity occurs. Dosage of TYZAVAN must be adjusted for patients with renal impairment *[see Dosage and Administration (2.3)]*. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity *[see Dosage and Administration (2.4)]*.

5.4 Severe Dermatologic Reactions

Severe dermatologic reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and linear IgA bullous dermatosis (LABD) have been reported in association with the use of vancomycin. Cutaneous signs or symptoms reported include skin rashes, mucosal lesions, and blisters.
Discontinue TYZAVAN at the first appearance of signs and symptoms of TEN, SJS, DRESS, AGEP, or LABD.

5.5 *Clostridioides difficile*-Associated Diarrhea (CDAD)

Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including vancomycin and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to 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 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 since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
Clinically significant serum concentrations have been reported in some patients being treated for active *C. difficile*-induced pseudomembranous colitis after multiple oral doses of vancomycin.
Prolonged use of TYZAVAN may result in the overgrowth of nonsusceptible microorganisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate

measures should be taken. In rare instances, there have been reports of pseudomembranous colitis due to *C. difficile* developing in patients who received intravenous vancomycin.

5.6 Hemorrhagic Occlusive Retinal Vasculitis (HORV)

Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for the prophylaxis of endophthalmitis.

5.7 Neutropenia

Reversible neutropenia has been reported in patients receiving vancomycin *[see Adverse Reactions (6.1)]*. Patients who will undergo prolonged therapy with vancomycin or those who are receiving concomitant drugs which may cause neutropenia should have periodic monitoring of the leukocyte count.

5.8 Phlebitis and Other Administration Site Reactions

Inflammation at the site of injection of vancomycin has been reported. Vancomycin is irritating to tissue and must be given by a secure intravenous route of administration to reduce the risk of local irritation and phlebitis.

Administration of vancomycin by intramuscular (IM), intraperitoneal, intrathecal (intralumbar or intraventricular), or intravitreal routes has not been approved and is not recommended. The safety and efficacy of vancomycin administered by the intrathecal (intralumbar or intraventricular) route or by the intraperitoneal route have not been established by adequate and well controlled trials.

Pain, tenderness, and necrosis occur with IM injection of vancomycin or with inadvertent extravasation. Thrombophlebitis may occur, the frequency and severity of which can be minimized by slow infusion of the drug and by rotation of venous access sites.

Intraperitoneal administration during continuous ambulatory peritoneal dialysis (CAPD) can result in chemical peritonitis. Manifestations range from cloudy dialysate alone to a cloudy dialysate accompanied by variable degrees of abdominal pain and fever. This syndrome appears to be resolved after discontinuation of intraperitoneal vancomycin.

About 60% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in 6 hours. Serum concentrations of about 10 mcg/mL are achieved by intraperitoneal injection of 30 mg/kg of vancomycin. However, the safety and efficacy of the intraperitoneal use of vancomycin has not been established in adequate and well-controlled trials.

5.9 Development of Drug-Resistant Bacteria

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

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions *[see Warnings and Precautions (5.1)]*
- Nephrotoxicity *[see Warnings and Precautions (5.2)]*
- Ototoxicity *[see Warnings and Precautions (5.3)]*
- Severe Dermatologic Reactions *[see Warnings and Precautions (5.4)]*
- *Clostridioides difficile*-Associated Diarrhea *[see Warnings and Precautions (5.5)]*

- Hemorrhagic Occlusive Retinal Vasculitis *[see Warnings and Precautions (5.6)]*
- Neutropenia *[see Warnings and Precautions (5.7)]*
- Phlebitis and Other Administration Site Reactions *[see Warnings and Precautions (5.8)]*.

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 following adverse reactions associated with the use of vancomycin were identified in clinical trials:

Immune System Disorders: Hypersensitivity reactions including anaphylaxis and "vancomycin infusion reactions"

Skin and Subcutaneous Tissue Disorders: Erythema (especially of the face, neck and upper torso) and pruritus which are manifestations of rashes including exfoliative dermatitis. Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Linear IgA bullous dermatosis (LABD)

Renal and Urinary Disorders: Acute kidney injury and interstitial nephritis

Ear and Labyrinth Disorders: Tinnitus, hearing loss, vertigo

Blood and Lymphatic System Disorders: Agranulocytosis, neutropenia, pancytopenia, leukopenia, thrombocytopenia, eosinophilia

Gastrointestinal Disorders: Pseudomembranous colitis

Cardiac Disorders: Cardiac arrest, chest pain

General Disorders and Administration Site Conditions: General discomfort, fever, chills, phlebitis, injection site irritation, injection site pain and necrosis following intramuscular injection, chemical peritonitis following intraperitoneal administration (TYZAVAN is not approved for intramuscular and intraperitoneal administration)

Laboratory Abnormalities: Elevated blood urea nitrogen, elevated serum creatinine

Musculoskeletal and Connective Tissue Disorders: Muscle pain

Nervous System Disorders: Dizziness

Respiratory, Thoracic and Mediastinal Disorders: Wheezing, dyspnea

Vascular Disorders: Hypotension, shock, vasculitis

6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of vancomycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders: Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP)

7 DRUG INTERACTIONS

7.1 Anesthetic Agents

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]*.

7.2 Piperacillin-Tazobactam

Studies have detected an increased incidence of acute kidney injury in patients administered concomitant piperacillin/tazobactam and vancomycin as compared to vancomycin alone. Monitor kidney function in patients receiving concomitant piperacillin/tazobactam and vancomycin. No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.

7.3 Ototoxic and/or Nephrotoxic Drugs

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs requires more frequent monitoring of renal function.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data on the use of this formulation of TYZAVAN (which includes the excipient NADA) in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available published data on vancomycin (without the excipient NADA) use in pregnancy during the second and third trimesters have not shown an association with adverse pregnancy related outcomes *(see Data)*. There are no available data on first trimester use of vancomycin in pregnant women to assess the risk of major birth defects or miscarriage.

Vancomycin alone did not show adverse developmental effects when administered intravenously to pregnant rats and rabbits during organogenesis at doses less than or equal to the recommended maximum human dose based on body surface area *(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.

Data

Human Data

Available data from postmarketing cases on use of this formulation of vancomycin injection (with the excipient NADA) in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or infant outcomes.

There are no available data on first trimester use of vancomycin (without the excipient NADA); however, available published data on use in pregnancy during the second and third trimesters have not shown an association with adverse pregnancy related outcomes.

A published study evaluated hearing loss and nephrotoxicity in infants of 10 pregnant intravenous drug users treated with vancomycin (formulation did not include the excipient NADA) for suspected or documented methicillin-resistant *Staphylococcus aureus* in the second or third trimester. The comparison groups were 10 uninfected non-intravenous drug-dependent patients, and 10 uninfected intravenous drug-dependent patients who served as substance abuse controls. No infant in the vancomycin exposed group had abnormal sensorineural hearing at 3 months of age or nephrotoxicity.

A published prospective study assessed outcomes in 55 pregnant women with a positive Group B streptococcus (GBS) culture and a high-risk penicillin allergy with resistance to clindamycin or unknown sensitivity who were administered vancomycin (formulation did not include the excipient NADA) at the time of delivery. Vancomycin dosing ranged from the standard 1 g intravenously every 12 hours to 20 mg/kg intravenous every 8 hours (maximum individual dose 2 g). No major adverse reactions were recorded either in the mothers or their newborns. None of the newborns had sensorineural hearing loss. Neonatal renal function was not examined, but all of the newborns were discharged in good condition.

Animal Data
Vancomycin did not cause fetal malformations when administered during organogenesis to pregnant rats (gestation days 6 to 15) and rabbits (gestation days 6 to 18) at doses less than or equal to the recommended maximum human dose (based on body surface area comparisons) of 200 mg/kg/day IV to rats or 120 mg/kg/day IV to rabbits. No effects on fetal weight or development were seen in rats at the highest dose tested or in rabbits given 80 mg/kg/day (approximately 1 and 0.8 times the recommended maximum human dose based on body surface area, respectively). Maternal toxicity was observed in rats (at doses 120 mg/kg and above) and rabbits (at 80 mg/kg and above).

Animal reproduction studies conducted in pregnant rabbits (gestation days 6 to 19) administered intravenous NADA at 1680 mg/kg (32 times the maximum daily human dose or greater based on AUC levels of NADA) resulted in fetal scoliosis and a spectrum of cardiovascular malformations. Increased incidence of delayed or incomplete ossifications of the metacarpals/metatarsals/phalanges and increased ossification (fused jugal/maxilla bones) were also observed in rabbits at 1680 mg/kg without maternal toxicity. No adverse developmental outcomes were observed in rabbits administered intravenous NADA at 560 mg/kg (11 times the maximum daily human dose based on AUC levels of NADA). In reproduction studies in pregnant rats (gestation days 6 to 17) administered intravenous NADA at 3780 mg/kg (20 times the maximum daily human dose based on AUC levels of NADA) no fetal adverse effects were observed. Maternal toxicity, including increased incidence of litter loss, was observed in rats at 3780 mg/kg *[see Clinical Pharmacology (12.3)]*.
No animal studies have been conducted to evaluate the potential reproductive and embryo-fetal effects of TYZAVAN (with the excipient NADA).

8.2 Lactation

Risk Summary
There are insufficient data to inform the levels of vancomycin in human milk. There are no data on the effects of vancomycin on the breastfed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TYZAVAN and any potential adverse effects on the breastfed infant from TYZAVAN or from the underlying maternal condition.

8.4 Pediatric Use

TYZAVAN is indicated in pediatric patients (1 month and older) for the treatment of septicemia, infective endocarditis, skin and skin structure infections, bone infections and lower respiratory tract infections for whom appropriate dosing with this formulation can be achieved *[see Indications and Usage (1.1 to 1.5) and Dosage and Administration (2.1, 2.3)]*.

Because of the limitations of the available strengths and administration requirements (i.e., administration of fractional doses is not recommended) of TYZAVAN, and to avoid unintentional overdose, this product is not recommended for use if a dose of Vancomycin Injection that does not equal 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g and 2 g is required, and an alternative formulation of vancomycin should be considered *[see Dosage and Administration (2.1, 2.3)]*.

More severe infusion related reactions related to vancomycin administration may occur in pediatric patients. In pediatric patients, monitor vancomycin serum concentration and renal function when administering TYZAVAN *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)].* Concomitant administration of vancomycin and intravenous anesthetic agents has been associated with erythema and histamine-like flushing in all patients including pediatric patients *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

TYZAVAN is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection *[see Dosage and Administration (2.2)]*, and it may be useful to monitor renal function *[see Warnings and Precautions (5.2)]*.

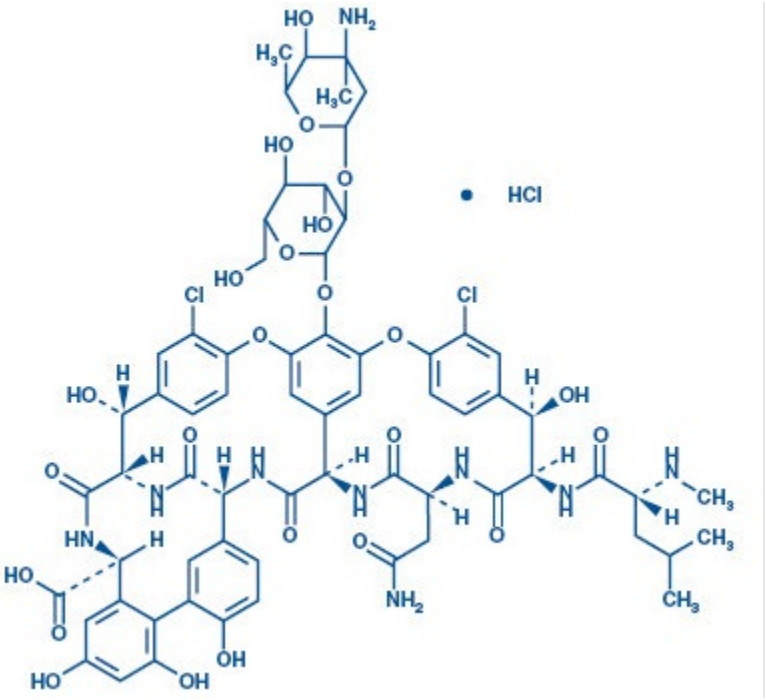
10 OVERDOSAGE

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Hemofiltration and hemoperfusion with polysulfone resin have been reported to result in increased vancomycin clearance.

For current information on the management of overdosage, contact the National Poison Control Center at 1-800-222-1222 or www.poison.org.

11 DESCRIPTION

TYZAVAN (Vancomycin Injection, USP), in single-dose flexible bags contain vancomycin as vancomycin hydrochloride. It is a tricyclic glycopeptide antibacterial drug derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). The molecular formula is $C_{66}H_{75}Cl_2N_9O_{24}$•HCl and the molecular weight is 1,485.71. The chemical name is (S_a)-(3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-44-{[2-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*lyxo*-hexopyranosyl)-β-D-glucopyranosyl]-oxy}-3-(carbamoylmethyl)-10,19-dichloro-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tetradecahydro-7,22,28,30,32-pentahydroxy-6-[(2*R*)-4-methyl-2-(methylamino]valeramido]-2,5,24,38,39-pentaoxo-22*H*-8,11:18,21-dietheno-23,36(iminometha-no)-13,16:31,35-dimetheno-1*H*,16*H*-[1,6,9]-oxadiazacyclohexadecino-[4,5-m][10,2,16]-benzoxa-diazacyclotetracosine-26-carboxylic acid, monohydrochloride. Vancomycin hydrochloride has the following structural formula:



TYZAVAN (Vancomycin Injection, USP), in single-dose flexible bags are sterile, nonpyrogenic premixed 100 mL, 150 mL, 200 mL, 250 mL, 300 mL, 350 mL or 400 mL solution containing 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g or 2 g vancomycin, respectively, as vancomycin hydrochloride. Each 100 mL of solution contains 1.36 g N-acetyl-D-alanine, 1.26 g L-lysine hydrochloride (monochloride) in water for injection. Hydrochloric acid and sodium hydroxide are used for pH adjustment. The pH is 4.5 to 5.5 and the osmolarity is 350 to 475 mOsmol/L.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Based on animal models of infection, the antimicrobial activity of vancomycin appears to correlate with the AUC/MIC (area under the concentration-time curve/minimum inhibitory concentration) ratio for certain pathogens, including methicillin resistant Staphylococcus aureus. The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials [2,3].

12.3 Pharmacokinetics

General Pharmacokinetics

In subjects with normal kidney function, multiple intravenous dosing of 1 g of vancomycin (15 mg/kg) infused over 60 minutes produces mean plasma concentrations of approximately 63 mcg/mL immediately after the completion of infusion, mean plasma concentrations of approximately 23 mcg/mL 2 hours after infusion, and mean plasma concentrations of approximately 8 mcg/mL 11 hours after the end of the infusion. Multiple dosing of 500 mg infused over 30 minutes produces mean plasma concentrations of about 49 mcg/mL at the completion of infusion, mean plasma concentrations of about 19 mcg/mL 2 hours after infusion, and mean plasma concentrations of about

10 mcg/mL 6 hours after infusion. The plasma concentrations during multiple dosing are like those after a single dose.

In healthy subjects administered a single 1g dose of TYZAVAN, geometric mean (geometric %CV) $AUC_{0\text{-}inf}$ values for NADA and vancomycin were 209 (19.6%) and 219 (13.7%) mcg*h/mL, respectively. Based on a population pharmacokinetic analysis, 1g TYZAVAN administered over 1.5 hours every 12 hours achieves a geometric mean (95% prediction interval) steady state $AUC_{0\text{-}24}$ exposure of 383 (277-547) and 382 (261-567) mcg*h/mL for NADA and vancomycin in healthy subjects, respectively.

Distribution

The volume of distribution ranges from 0.3 to 0.43 L/kg after intravenous administration.
Vancomycin is approximately 55% serum protein bound as measured by ultrafiltration at vancomycin serum concentrations of 10 to 100 mcg/mL. After intravenous administration of vancomycin, inhibitory concentrations are present in pleural, pericardial, ascitic, and synovial fluids; in urine; in peritoneal dialysis fluid; and in atrial appendage tissue. Vancomycin does not readily diffuse across normal meninges into the spinal fluid; but, when the meninges are inflamed, penetration into the spinal fluid occurs.

Elimination

Mean plasma clearance is about 0.058 L/kg/h, and mean renal clearance is about 0.048 L/kg/h. The mean elimination half-life of vancomycin from plasma is 4 to 6 hours in subjects with normal renal function. In anephric patients, the mean elimination half-life is 7.5 days. Total body and renal clearance of vancomycin may be reduced in the elderly.

Metabolism

There is no apparent metabolism of the vancomycin.

Excretion

In the first 24 hours after intravenous administration, about 75% of an administered dose of vancomycin is excreted in urine by glomerular filtration. Renal impairment slows excretion of vancomycin.

In the first 48 hours after intravenous administration of a single 1 g dose of TYZAVAN, the percent excreted unchanged in urine was approximately 80% for NADA.

12.4 Microbiology

Mechanism of Action

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis.

Resistance

Vancomycin is not active *in vitro* against gram-negative bacilli, mycobacteria, or fungi. There is no cross-resistance between vancomycin and other antibacterials.

Interaction with Other Antimicrobials

The combination of vancomycin and an aminoglycoside acts synergistically *in vitro* against many isolates of *Staphylococcus aureus*, *Streptococcus gallolyticus* (previously known as *Streptococcus bovis*), *Enterococcus* spp, and the viridans group streptococci.

Antimicrobial Activity

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

Aerobic bacteria

Gram-positive bacteria
Corynebacterium spp.
Enterococcus spp. (including *Enterococcus faecalis*)
Staphylococcus aureus (including methicillin-resistant and methicillin-susceptible isolates)
Coagulase negative staphylococci (including *S.epidermidis* and methicillin-resistant isolates)
Streptococcus gallolyticus (previously known as *Streptococcus bovis*)
Viridans group streptococci

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

Aerobic bacteria

Gram-positive bacteria
Listeria monocytogenes
Streptococcus pyogenes
Streptococcus pneumoniae
Streptococcus agalactiae

Anaerobic bacteria

Gram-positive bacteria
Actinomyces species
Lactobacillus species

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

Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of vancomycin was found in standard laboratory tests. No definitive fertility studies have been performed.

13.2 Animal Toxicology and/or Pharmacology

In animal studies, hypotension and bradycardia occurred in dogs receiving an intravenous infusion of vancomycin 25 mg/kg, at a concentration of 25 mg/mL and an infusion rate of 13.3 mL/min.

15 REFERENCES

1. Byrd RA., Gries CL, Buening M.: Developmental Toxicology Studies of Vancomycin Hydrochloride Administered Intravenously to Rats and Rabbits. Fundam Appl Toxicol 1994; 23: 590-597.
2. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clinical Infectious Diseases. 2006;42 (Supplement_1): S35-S39.
3. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Clinical Infectious Diseases. 2020;71(6):1361-1364.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TYZAVAN (Vancomycin Injection, USP)is supplied as a ready to use clear, colorless to light brown solution in single-dose flexible bags containing 500 mg, 750 mg, 1 g, 1.25 g, 1.5 g, 1.75 g and 2 g vancomycin in 100 mL, 150 mL, 200 mL, 250 mL, 300 mL, 350 mL and 400 mL of liquid (consists of water for injection together with the excipients NADA and lysine) *[see Description (11)]*. The flexible bags are supplied in sealed aluminum overpouches. The bags are supplied in the following packages described in table 1 below:

Table 1: TYZAVAN PACKAGE INFORMATION

Strength of TYZAVAN	NDC number	Packaging configuration
500 mg/100 mL (5 mg/mL)	0143-9471-06	Carton of six bags
500 mg/100 mL (5 mg/mL)	0143-9471-12	Carton of twelve bags
750 mg/150 mL (5 mg/mL)	0143-9468-06	Carton of six bags
750 mg/150 mL (5 mg/mL)	0143-9468-12	Carton of twelve bags
1 g/200 mL (5 mg/mL)	0143-9472-06	Carton of six bags
1 g/200 mL (5 mg/mL)	0143-9472-12	Carton of twelve bags
1.25 g/250 mL (5 mg/mL)	0143-9466-06	Carton of six bags
1.5 g/300 mL (5 mg/mL)	0143-9469-06	Carton of six bags
1.75 g/350 mL (5 mg/mL)	0143-9467-06	Carton of six bags
2 g/400 mL (5 mg/mL)	0143-9470-06	Carton of six bags

16.2 Storage

Store at 15°C to 25°C (59°F to 77ºF), in original package. Use within 28 days of removal from aluminum overpouch.

17 PATIENT COUNSELING INFORMATION

Infusion Reactions During or After Intravenous Use

Advise patients that generalized skin redness, skin rash, itching, flushing, muscle pain, chest pain, shortness of breath, wheezing, or dizziness may occur during TYZAVAN infusion. These reactions can be lessened or prevented by infusing the drug over at least 60 minutes *[see Warnings and Precautions (5.1)]*.

Acute Kidney Injury

Advise patients that TYZAVAN can result in kidney damage and that blood tests are required to monitor vancomycin blood levels and kidney function during therapy *[see Warnings and Precautions (5.2)]*.

Hearing Loss or Balance Problems

Advise patients that TYZAVAN may result in decreased hearing and to report hearing loss or balance problems to their health care provider *[see Warnings and Precautions (5.3)]*.

Severe Dermatologic Reactions

Advise patients about the signs and symptoms of serious skin manifestations. Instruct patients to stop TYZAVAN immediately and promptly report the first signs or symptoms of skin rash, mucosal lesions or blisters to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Diarrhea

Diarrhea is a common problem caused by antibacterial drugs, including vancomycin, which usually ends when the antibacterial 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 having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible *[see Warnings and Precautions (5.1)]*.

Antibacterial Resistance

Patients should be counseled that antibacterial drugs including TYZAVAN, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When TYZAVAN 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 TYZAVAN or other antibacterial drugs in the future.

Manufactured for:
Hikma Pharmaceuticals USA, Inc.
Berkeley Heights, NJ 07922

Made in Switzerland

L130USTZV00