PV 1985 AMP

VANCOCIN® HCl
Vancomycin Hydrochloride
Capsules, USP
Pulvules®

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

This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancocin® HCl must be given orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Orally administered Vancocin HCl is not effective for other types of infection.

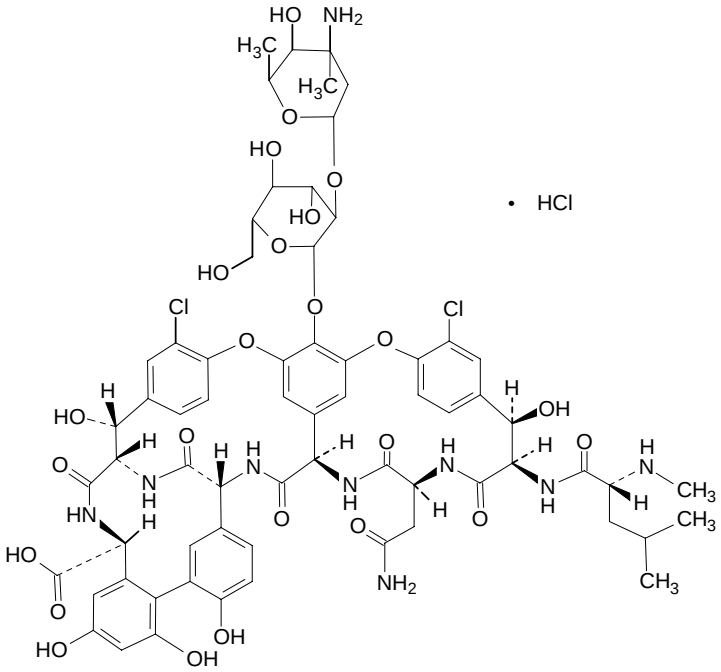
Parenteral administration of Vancocin HCl is *not* effective for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. If parenteral vancomycin therapy is desired, use Vancocin® HCl (Sterile Vancomycin Hydrochloride, USP), IntraVenous, and consult package insert accompanying that preparation.

DESCRIPTION

Pulvules® Vancocin® HCl (Vancomycin Hydrochloride Capsules, USP) contain chromatographically purified vancomycin hydrochloride, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24}$•HCl. The molecular weight of vancomycin hydrochloride is 1485.73; 500 mg of the base is equivalent to 0.34 mmol.

The Pulvules contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The Pulvules also contain F D & C Blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.

Vancomycin hydrochloride has the following structural formula:



CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. Additional data using an oral solution follow. In anephric patients with no inflammatory bowel disease, blood concentrations of vancomycin were barely measurable (0.66 μg/mL) in 2 of 5 subjects who received 2 g of Vancocin HCl for Oral Solution daily for 16 days. No measurable blood concentrations were attained in the other 3 patients. With doses of 2 g daily, very high concentrations of drug can be found in the feces (>3100 mg/kg) and very low concentrations (<1 μg/mL) can be found in the serum of patients with normal renal function who have pseudomembranous colitis. Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. After multiple-dose oral administration of vancomycin, measurable serum concentrations may infrequently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.

Microbiology

The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics.

NOTE: The oral form of vancomycin is effective only for the infections noted in the **INDICATIONS AND USAGE** section. The oral form is ***not*** effective for any other type of infection.

Vancomycin has been shown to be active against most strains of the following microorganisms in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Staphylococcus aureus (including methicillin-resistant strains) associated with enterocolitis

Anaerobic gram-positive microorganisms

Clostridium difficile antibiotic-associated pseudomembranous colitis

INDICATIONS AND USAGE

Vancocin HCl Pulvules may be administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Parenteral administration of Vancocin HCl is not effective for the above indications; therefore, Vancocin HCl must be given orally for these indications. **Orally administered Vancocin HCl is not effective for other types of infection.**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Vancocin HCl and other antibacterial drugs, Vancocin HCl 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.

CONTRAINDICATION

Vancocin HCl is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS

General

Prescribing Vancocin HCl 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.

Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis; therefore, monitoring of serum concentrations may be appropriate in some instances, e.g., in patients with renal insufficiency and/or colitis.

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. (See package insert accompanying the intravenous preparation.) The risk is greater if renal impairment is present. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

Ototoxicity has occurred in patients receiving Vancocin HCl. It may be transient or permanent. It has been reported mostly in patients who have been given excessive intravenous doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

When patients with underlying renal dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated, serial monitoring of renal function should be performed.

Use of vancomycin may result in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Information for Patients

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term carcinogenesis studies in animals have been conducted.

At concentrations up to 1000 μg/mL, vancomycin had no mutagenic effect *in vitro* in the mouse lymphoma forward mutation assay or the primary rat hepatocyte unscheduled DNA synthesis assay. The concentrations tested *in vitro* were above the peak plasma vancomycin concentrations of 20 to 40 μg/mL usually achieved in humans after slow infusion of the maximum recommended dose of 1 g. Vancomycin had no mutagenic effect *in vivo* in the Chinese hamster sister chromatid exchange assay (400 mg/kg IP) or the mouse micronucleus assay (800 mg/kg IP).

No definitive fertility studies have been conducted.

Pregnancy

Teratogenic Effects — Pregnancy Category B — The highest doses of vancomycin tested were not teratogenic in rats given up to 200 mg/kg/day IV (1180 mg/m^2 or 1 times the recommended maximum human dose based on a mg/m^2 basis) or in rabbits given up to 120 mg/kg/day IV (1320 mg/m^2 or 1.1 times the recommended maximum human dose based on a mg/m^2 basis). No effects on fetal weight or development were seen in rats at the highest dose tested or in rabbits given 80 mg/kg/day (880 mg/m^2 or 0.74 times the recommended maximum human dose based on mg/m^2).

In a controlled clinical study, the potential ototoxic and nephrotoxic effects of Vancocin HCl on infants were evaluated when the drug was administered intravenously to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancocin HCl was found in cord blood. No sensorineural hearing loss or nephrotoxicity attributable to Vancocin HCl was noted. One infant whose mother received Vancocin HCl in the third trimester experienced conductive hearing loss that was not attributed to the administration of Vancocin HCl. Because the number of patients treated in this study was limited and Vancocin HCl was administered only in the second and third trimesters, it is not known whether Vancocin HCl causes fetal harm. Because animal reproduction studies are not always predictive of human response, Vancocin HCl should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Vancomycin is excreted in human milk based on information obtained with the intravenous administration of Vancocin HCl. However, systemic absorption of vancomycin is very low following oral administration of Vancocin HCl Pulvules (*see* **CLINICAL PHARMACOLOGY**). It is not known whether oral vancomycin is excreted in human milk, as no studies of vancomycin concentration in human milk after oral administration have been done. Caution should be exercised when Vancocin HCl is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Nephrotoxicity — Rarely, renal failure, principally manifested by increased serum creatinine or BUN concentrations, especially in patients given large doses of intravenously administered Vancocin HCl has been reported. Rare cases of interstitial nephritis have been reported. Most of these have occurred in patients who were given aminoglycosides concomitantly or who had preexisting kidney dysfunction. When Vancocin HCl was discontinued, azotemia resolved in most patients.

Ototoxicity — A few dozen cases of hearing loss associated with intravenously administered Vancocin HCl have been reported. Most of these patients had kidney dysfunction or a preexisting

hearing loss or were receiving concomitant treatment with an ototoxic drug. Vertigo, dizziness, and tinnitus have been reported rarely.

Hematopoietic — Reversible neutropenia, usually starting 1 week or more after onset of intravenous therapy with Vancocin HCl or after a total dose of more than 25 g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when Vancocin HCl is discontinued. Thrombocytopenia has rarely been reported.

Miscellaneous — Infrequently, patients have been reported to have had anaphylaxis, drug fever, chills, nausea, eosinophilia, rashes (including exfoliative dermatitis), Stevens-Johnson syndrome, toxic epidermal necrolysis, and rare cases of vasculitis in association with the administration of Vancocin HCl.

A condition has been reported that is similar to the IV-induced syndrome with symptoms consistent with anaphylactoid reactions, including hypotension, wheezing, dyspnea, urticaria, pruritus, flushing of the upper body ("Red Man Syndrome"), pain and muscle spasm of the chest and back. These reactions usually resolve within 20 minutes but may persist for several hours.

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.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

DOSAGE AND ADMINISTRATION

Adults — Oral Vancocin HCl is used in treating antibiotic-associated pseudomembranous colitis caused by *C. difficile* and staphylococcal enterocolitis. Vancocin HCl is not effective by the oral route for other types of infections. The usual adult total daily dosage is 500 mg to 2 g administered orally in 3 or 4 divided doses for 7 to 10 days.

Pediatric Patients — The usual daily dosage is 40 mg/kg in 3 or 4 divided doses for 7 to 10 days. The total daily dosage should not exceed 2 g.

HOW SUPPLIED

Vancocin® HCl Pulvules® (or Vancomycin Hydrochloride Capsules, USP) are available in:

The 125 mg* Pulvules have an opaque blue cap and opaque brown body imprinted with "3125" on the cap and "VANCOCIN HCL 125 MG" on the body in white ink. They are available in:

ID†20	NDC 0002-3125-42 (PU3125)

The 250 mg* Pulvules have an opaque blue cap and opaque lavender body imprinted with "3126" on the cap and "VANCOCIN HCL 250 MG" on the body in white ink. They are available in:

ID†20	NDC 0002-3126-42 (PU3126)

Store at controlled room temperature, 59° to 86°F (15° to 30°C).

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*Equivalent to vancomycin.
†Identi-Dose® (unit dose medication, Lilly).

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