1.4.3 Package Insert (PI)

Enclosed in the following pages.

VANCONEX

Vancomycin for Injection USP 500 mg/Vial & 1 g/Vial

Lyophilised powder

VANCONEX (Vancomycin for Injection USP 500 mg/Vial)

Each vial contains Vancomycin Hydrochloride USP equivalent to Vancomycin 500 mg.

VANCONEX (Vancomycin for Injection USP 1 g/Vial)

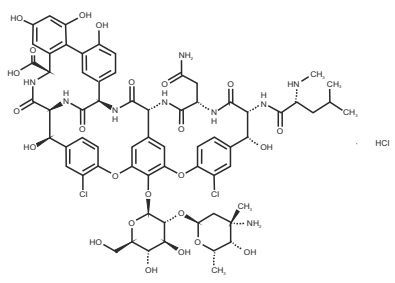
Each vial contains Vancomycin Hydrochloride USP equivalent to Vancomycin 1 g.

DESCRIPTION

Vancomycin Hydrochloride for Injection is a lyophilized powder, for preparing intravenous (IV) infusions, in vials containing the equivalent of 500 mg or 1 g vancomycin base. 500 mg of the base is equivalent to 0.34 mmol, and 1 g of the base is equivalent to 0.67 mmol. When reconstituted with Sterile Water for Injection to a concentration of 50 mg/mL, the pH of the solution is between 2.5 and 4.5. Vancomycin Hydrochloride for Injection should be administered intravenously in diluted solution. After reconstitution further dilution is required before use.

Vancomycin Hydrochloride is a chromatographically purified tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*) and has the molecular formula $C_{66}H_{75}Cl_2N_9O_{24}$.HCl. The molecular weight is 1485.71; 500 mg of the base is equivalent to 0.34 mmol, and 1 g of the base is equivalent to 0.67 mmol.

Vancomycin Hydrochloride has the following structural formula:



Vancomycin Hydrochloride is a white to tan lyophilized powder. When reconstituted with Sterile Water for Injection, USP, it forms a clear, light to dark tan solution. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. This product is oxygen sensitive.

Each vial contains Vancomycin Hydrochloride USP is equivalent to Vancomycin 500 mg

Each vial contains Vancomycin Hydrochloride USP is equivalent to Vancomycin 1 g.

INDICATIONS

Vancomycin is indicated for the treatment of serious or severe infections caused by susceptible strains of methicillin-resistant (beta-lactam resistant) staphylococci. It is indicated for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, including the penicillins or cephalosporins, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs. Vancomycin is indicated for initial therapy when methicillin-resistant staphylococci are suspected, but after susceptibility data are available, therapy should be adjusted accordingly.

Vancomycin's effectiveness has been documented in other infections due to staphylococci, including septicemia, bone infections, lower respiratory tract infections, skin and skin structure infections. When staphylococcal infections are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

Specimens for bacteriologic cultures should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to vancomycin.

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

DOSAGE AND ADMINISTRATION

An infusion rate of 10mg/min or less is associated with fewer infusions-related events, Infusion-related events are related to both concentration and rate of administration of vancomycin. Concentrations of no more than 5 mg/ml and rates of no more than 10mg/min are recommended in adults (see also age-specific recommendations).

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 events. Infusion-related events may occur, however, at any rate or concentration.

Patients with normal renal function

Adults

The usual daily intravenous dose is 2g divided either as 500mg every 6 hours or 1g every 12 hours. Each dose should be administered at no more than 10mg/min, or over a period of at least 60 minutes, whichever is longer. Other patient factors, such as age or obesity, may call for modification of the usual intravenous daily dose.

Pediatric patients

The usual intravenous dosage of vancomycin 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 may be warranted in these patients.

Neonates

In pediatric patients up to the age of 1 month, the total daily intravenous dosage may be lower. In neonates, an initial dose of 15 mg/kg is suggested, followed by 10 mg/kg every 12 hours for neonates in the first week of life and every 8 hours thereafter up to the age of one month. Each dose should be administered over 60 minutes. In premature infants, vancomycin clearance decreases as postconceptional age decreases. Therefore, longer dosing intervals may be necessary in premature infants. Close monitoring of serum concentrations of vancomycin is recommended in these patients.

Patients with impaired renal function and elderly patients

Dosage adjustment must be made in patients with impaired renal function. In premature infants and in the elderly, greater dosage reductions than expected may be necessary because of decreased renal function. Measurement of vancomycin serum concentrations can be helpful in optimizing therapy, especially in seriously ill patients with changing renal function. Vancomycin serum concentrations can be determined by use of microbiologic assay, radioimmunoassay, fluorescence polarization immunoassay, fluorescence immunoassay, or high-pressure liquid chromatography. If creatinine clearance can be measured or estimated accurately, the dosage for most patients with renal impairment can be calculated using the following table.

The dosage of vancomycin per day in mg is about 15 times the glomerular filtration rate in ml/min.

Dosage table for vancomycin in patients with impaired renal function

Creatinine Clearance mL/min	Vancomycin Dose mg/24 h
100	1545
90	1390
80	1235
70	1080
60	925
50	770
40	620
30	465
20	310
10	155

The initial dose should be no less than 15 mg/kg, even in patients with mild to moderate renal insufficiency.

The table is not valid for functionally anephric patients. For such patients, an initial dose of 15mg/kg of body weight should be given to achieve prompt therapeutic serum concentrations. The dose required to maintain stable concentrations is 1.9 mg/kg/24h. In patients with marked renal impairment, it may be more convenient to be given maintenance doses of 250 to 1000mg once every several days rather than administering the drug on a daily basis. In anuria, a dose of 1000 mg every 7 to 10 days has been recommended.

When only the serum creatinine concentration is known, the following formula (based on sex, weight and age of the patient) may be used to calculate creatinine clearance. Calculated creatinine clearance (ml/min) are only estimates. The creatinine clearance should be measured promptly.

$$\text{Men: } \frac{\text{Weight (kg) x (140 – age in years)}}{\text{72 x serum creatinine concentration (mg/dL)}}$$

Women: 0.85 x above value

The serum creatinine must represent a steady state of renal function. Otherwise the estimated value for creatinine clearance is not valid. Such a calculated clearance is an overestimate of actual clearance in patients with conditions: 1) characterized by decreasing renal function, such as shock, severe heart failure or oliguria; 2) in which a normal relationship between muscle mass and total body weight is not present, such as obese patients or those with liver disease, edema or ascites; and 3) accompanied by debilitation, malnutrition or inactivity.

The safety and efficacy of vancomycin administration by the intrathecal (intralumbar or intraventricular) routes have not been established. Intermittent infusion is the recommended method of administration."

Compatibility with other Drugs and Intravenous Fluids

The following diluents are physically and chemically compatible (with 4g/L Vancomycin Hydrochloride):

5% Dextrose Injection

5% Dextrose Injection and 0.9% Sodium Chloride Injection

Lactated Ringer's Injection,

5% Dextrose, Lactated Ringer's Injection

0.9% Sodium Chloride Injection,

Good professional practice suggests that compounded admixtures should be administered as soon after preparation as is feasible.

Vancomycin solution has a low pH and may cause physical instability of other compounds.

Mixtures of solutions of vancomycin and beta-lactam antibiotics 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 administrations of these antibiotics. It is also recommended to dilute solutions of vancomycin to mg/mL or less.

Although intravitreal injection is not an approved route of administration for vancomycin, precipitation has been reported after intravitreal injection of vancomycin and ceftazidime for endophthalmitis using different syringes and needles. The precipitates dissolved gradually, with complete clearing of the vitreous cavity over two months and with improvement of visual acuity.

Preparation and Stability

At the time of use, reconstitute the vials of Vancomycin Hydrochloride for Injection , USP with Sterile Water for Injection to a concentration of 50 mg of vancomycin/mL (see following table for volume of diluent).

Concentration/Vial	Volume of Diluent
500 mg	10 mL
1 g	20 mL

After reconstitution, the vials may be stored in a refrigerator for 96 hours without significant loss of potency.

Reconstituted solutions of vancomycin (500 mg/10 mL) must be further diluted with at least 100 mL of a suitable infusion solution. For doses of 1gram (20mL), at least 200 mL of solution must be used. The desired dose, diluted in this manner, should be administered by intermittent IV infusion over a period of at least 60 minutes.

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

CONTRAINDICATIONS

Vancomycin Hydrochloride for Injection, is contraindicated in patients with known hypersensitivity to this antibiotic.

DRUG INTERACTIONS

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions.

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, or cisplatin, when indicated, requires careful monitoring.

There have been reports that the frequency of infusion-related events increases with the concomitant administration of anaesthetic agents. Infusion-related events may be minimised by the administration of vancomycin as a 60-minute infusion prior to anaesthetic induction.

There is an increase potential of neuromuscular blockage with concomitant administration of vancomycin and neuromuscular blocking agents.

WARNINGS AND PRECAUTIONS

Rapid bolus administration (e.g. over several minutes) may be associated with exaggerated hypotension, including shock, and, rarely cardiac arrest, histamine like responses and maculopapular or erythematous rash ("red man's syndrome" or "red neck syndrome"). Vancomycin should be infused in a dilute solution over a period of not less than 60 minutes to avoid rapid infusion-related reactions. Stopping the infusion usually results in a prompt cessation of these reactions (see sections "Dosage and administration" and "Adverse Reactions").

Due to its potential ototoxicity and nephrotoxicity, vancomycin should be used with care in patients with renal insufficiency and the dose should be reduced according to the degree of renal impairment. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. Blood levels should be monitored and renal function tests should be performed regularly.

Vancomycin should also be avoided in patients with previous hearing loss. If it is used in such patients, the dose should be regulated, if possible, by periodic determination of the drug level in the blood. Deafness may be preceded by tinnitus.

The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment

Use in paediatrics: In premature neonate and young infants, it may be appropriate to confirm desired vancomycin serum concentrations. Concomitant administration of vancomycin and anaesthethic agents has been associated with erythema and histamine-like flushing in children.

Use in the elderly: The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentration if dosage is not adjusted (see "Dosage and administration").

Precautions

Regular monitoring of the blood levels of vancomycin is indicated in longer-term use, particularly in patients with renal dysfunction or impaired faculty of hearing as well as in concurrent administration of nephrotoxic or ototoxic substances, respectively.

Doses should be titrated on the basis of serum levels. Blood levels should be monitored and renal function tests performed regularly.

Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and vancomycin blood levels. All patients receiving the drug should have periodic haematological studies, urine analysis and renal function tests.

Vancomycin is very irritating to tissue, and causes injection site necrosis when injected intramuscularly; it must be infused intravenously. Injection site pain and thrombophlebitis occur in many patients receiving vancomycin and are occasionally severe.

The frequency and severity of thrombophlebitis can be minimised by administering the drug slowly as a dilute solution (2.5 to 5.0 g/l) and by rotating the sites of infusion.

Prolonged use of vancomycin may result in the overgrowth of non-susceptible organisms. 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.

As cases of cross hypersensitivity have been reported, Vancomycin must be administered with care in patients with known hypersensitivity to Teicoplanin.

Pseudomembranous colitis

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents including vancomycin, and may range in severity from mild to life-threatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C.difficile colitis.

ADVERSE REACTIONS

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed below are defined using the following MedDRA:

Very common	≥1/10
Common	≥1/100 to < 1/10
Uncommon	≥1/1,000 to < 1/100
Rare	≥1/10,000 to <1/1,000
Very rare	<1/10,000
Not known	Frequency cannot be estimated from the available data.

Intravenous Infusion:

The most common adverse reactions are phlebitis and pseudo-allergic reactions in connection with too rapid intravenous infusion of vancomycin.

Hematopoietic: Reversible neutropenia, usually starting one week or more after onset of therapy with vancomycin or after a total dosage of more than 25g, has been reported for several dozen patients. Neutropenia appears to be promptly reversible when vancomycin is discontinued. Thrombocytopenia has rarely been reported.

Although a causal relationship has not been established, reversible agranulocytosis (granulocytes < 500/mm^3) has been reported rarely.

Phlebitis: Inflammation at the injection site has been reported.

Miscellaneous: Infrequently, patients have been reported to have had anaphylaxis, drug fever, nausea, chills, eosinophilia, rashes including exfoliative dermatitis, Steven-Johnson syndrome, and vasculitis in association with administration of vancomycin. Chemical peritonitis has been reported following intraperitoneal administration of vancomycin.

Blood and the lymphatic system disorder
Rare: Thrombocytopenia, neutropenia, agranulocy.toses, eosinophilia

Immune system disorders
Rare: anaphylactic reactions, hypersensitivity reactions

Ear and labyrinth disorders
Uncommon: Transient or permanent loss of hearing
Rare: Tinnitus, dizziness

Cardiac disorders
Very rare: cardiac arrest

Vascular disorders
Common: Decrease in blood pressure
Rare: Vasculitis

Respiratory, thoracic, and mediastinal disorders
Common: Dyspnoea, stridor

Gastrointestinal disorders
Rare: Nausea
Very rare: Pseudomembranous enterocolitis

Skin and subcutaneous tissue disorders
Common: Exanthema and mucosal inflammation, pruritus, urticaria
Very rare: Exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, Linear IgA bullous dermatosis

Dimensions: 200 x 400 mm

Colour: Black

Not known: drug rash with eosinophilia and systemic symptoms

Renal and urinary disorders
Common: Renal insufficiency manifested primarily by increased serum creatinine
Rare: Interstitial nephritis, acute renal failure

General disorders and administration site conditions
Common: Phlebitis, redness of the upper body and the face
Rare: Drug fever, shivering; Pain in the chest and back muscles

Infusion related events
During or shortly after rapid infusion anaphylactoid reactions may occur, including hypotension, dyspnea, urticaria or pruritus. Redness of the skin on the upper body (Red man syndrome), pain and cramps in chest or back muscle can occur.

The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Vancomycin should be infused slowly (for more than 60 minutes – see section "Warnings and precautions".)

Ototoxicity may be reversible or permanent, and has been reported mainly in patients given an overdose in patients with a history of reduced hearing, and with concomitant therapy with other ototoxic drugs, such as aminoglycosides.

Pregnancy

Teratogenic Effects

Pregnancy Category C

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

Nursing Mothers

Vancomycin Hydrochloride for Injection, is excreted in human milk. Caution should be exercised when Vancomycin Hydrochloride for Injection, is administered to a nursing woman. Because of the potential for adverse events, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
In pediatric patients, it may be appropriate to confirm desired vancomycin serum concentrations.

Concomitant administration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing in pediatric patients.

Geriatric Use
The natural decrement of glomerular filtration with increasing age may lead to elevated vancomycin serum concentrations if dosage is not adjusted. Vancomycin dosage schedules should be adjusted in elderly patients.

Information for Patients

Patients should be counselled that antibacterial drugs including Vancomycin Hydrochloride for injection, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Vancomycin Hydrochloride for injection, USP 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 Vancomycin Hydrochloride for injection, USP or other antibacterial drugs in the future.

Diarrhoea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, 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 antibiotic. If this occurs, patients should contact their physician as soon as possible.

OVERDOSE

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.

The median lethal intravenous dose is 319 mg/kg in rats and 400 mg/kg in mice.

In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group, "antibacterials for systemic use Glycopeptide Antibacterials", "ATC Code: J01XA01".

Mode of action

Vancomycin is a tricylic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units. The drug is bactericidal for dividing microorganisms.

PK/PD relationship

Vancomycin activity is considered to be time-dependent.

Mechanism of resistance

Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various van gene complexes which modifies the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly. Cross-resistance with teicoplanin has been reported for some van genes. Van genes have rarely been found in Staphylococcus aureus, where changes in cell wall structure result in "intermediate" susceptibility, which is most commonly heterogeneous.

Susceptibility:

Vancomycin is particularly active against gram-positive bacteria, such as staphylococci, streptococci, enterococci, pneumococci, and clostridia and diphtheroides. Gram-negative bacteria are resistant. The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Pharmacokinetic properties

Absorption

Vancomycin is administered intravenously for the treatment of systemic infections. In the case of patients with normal renal function, intravenous infusion of multiple doses of 1g vancomycin (15 mg/kg) for 60 minutes produces approximate average plasmatic concentrations of 50-60 mcg/ml, 20-25 mcg/ml and 5-10 mcg/ml, immediately 2 hours and 11 hours after completing the infusion, respectively. Intravenous infusion of multiple doses of 500mg for 30 minutes produces average plasmatic concentrations of around 40-50 mg/l, 19-20 mg/l and 10-11 mg/l immediately, 2 hours and 6 hours after completing the infusion, respectively. The plasmatic levels obtained after multiple doses are similar to those achieved after a single dose.

In case of oral use, high-polar vancomycin is virtually not absorbed. It appears after oral administration in active form in the stool, and is therefore a suitable chemotherapeutic for pseudomembranous colitis and staphylococcal colitis.

Distribution

At serum concentrations of vancomycin of 10 mg/l to 100 mg/l, the binding of the drug to plasma proteins is approximately 30-55%, measured by ultra-filtration.

After intravenous administration of vancomycin hydrochloride, inhibitory concentrations are found in the pleural, pericardial, ascitic and sinovial fluids, in the urine and the peritoneal dialysis fluid and in the tissue of the atrial appendix.

In non-inflamed meninges vancomycin passes the blood-brain barrier only to a low extent.

Elimination

The elimination half-life of vancomycin is 4 to 6 hours in patients with normal renal function. In the first 24 hours, approximately 80% of an administered dose of vancomycin is excreted in the urine through glomerular filtration. Renal dysfunction delays the excretion of vancomycin. In anephric patients, the mean half-life is 7.5 days. There is very little metabolism of the drug. Approximately 35-65% of an intraperitoneal dose of vancomycin administered during peritoneal dialysis is absorbed systemically in six hours. Serum concentrations of approximately 8 mg/litre are achieved through intraperitoneal injection of 30 mg/kg vancomycin. Although the vancomycin is not eliminated efficiently by haemodialysis or peritoneal dialysis, there have been reports of an increase in vancomycin clearance with haemoperfusion and haemofiltration. Total systemic and renal clearance of vancomycin may be reduced in persons of advanced age."

HOW SUPPLIED
VANCONEX (Vancomycin Hydrochloride for Injection USP 500 mg/Vial)
White to tan lyophilized cake or powder present in 20 mL clear USP Type I tubular glass vial with 20 mm grey bromobutyl lyophilization rubber stopper and 20 mm sky blue colored flip off seal. When reconstituted as directed the solution should be clear, light to dark tan colored solution.

VANCONEX (Vancomycin Hydrochloride for Injection USP 1 g/ Vial)
White to tan lyophilized cake or powder present in 30 mL clear USP Type I tubular glass vial with 20 mm grey bromobutyl lyophilization rubber stopper and 20 mm grey colored flip off seal. When reconstituted as directed the solution should be clear, light to dark tan colored solution.

PACKAGING INFORMATION
VANCONEX (Vancomycin Hydrochloride for Injection USP 500 mg /Vial, 1g/Vial)
Vancomycin Hydrochloride Injection is available in sterile single-use vials individually packed in a carton.

STORAGE:
Store below 30°C, protect from light.

PACK STYLE:
500 mg : 20 mL clear tubular glass - 10's vial
1g : 30 mL clear tubular glass - 10's vial

Product Owner:
HETERO LABS LIMITED
7-2-A 2, Hetero Corporate, Industrial Estates,
Sanath nagar, Hyderabad - 500 018, INDIA

Manufactured by:
Aspiro
ASPIRO PHARMA LIMITED
Survey No. 321, Biotech Park,
Phase-III, Karkapatla Village,
Markook Mandal, Siddipet Dist.,
Telangana State-502281, INDIA

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