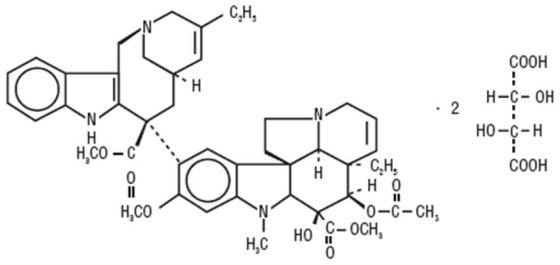
ZYROLBINE

VINORELBINE INJECTION I.P.

COMPOSITION:
Each ml contains:
Vonorelbine Tartarate I.P
Equivalent to Vinorelbine 10mg
Water for Injections I.P.

DESCRIPTION
Vinorelbine is asemisynthetic vinca alkaloid, derived from Vinbastine with broad spectrum of antitumor activity. It is a derivative of Vinblastine. However, Vinorelbine may have less neurotoxicity than Vincristine.



CLINICAL PHARMACOLOGY
ZYROLBINE is a vinca alkaloid that interferes with microtubule assembly. The vinca alkaloids are structurally similar compounds comprised of 2 multiringed units, vindoline and catharanthine. Unlike other vinca alkaloids, the catharanthine unit is the site of structural modification for ZYROLBINE. The antitumor activity of ZYROLBINE is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Like other vinca alkaloids, ZYROLBINE may also interfere with: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulindependent Ca++-transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. In intact tectal plates from mouse embryos, ZYROLBINE, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration (2 µM), inducing a blockade of cells at metaphase. Vincristine produced depolymerization of axonal microtubules at 5 µM, but vinblastine and ZYROLBINE did not have this effect until concentrations of 30 µM and 40 µM, respectively. These data suggest relative selectivity of ZYROLBINE for mitotic microtubules.

Pharmacokinetics:
The pharmacokinetics of ZYROLBINE were studied in 49 patients who received doses of 30 mg/m2 in 4 clinical trials. Doses were administered by 15- to 20-minute constant-rate infusions. Following intravenous administration, ZYROLBINE concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of ZYROLBINE from peripheral compartments. The terminal phase half-life averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/hr/kg. Steady-state volume of distribution (Vss) values range from 25.4 to 40.1 L/kg.
ZYROLBINE demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in pooled human plasma over a concentration range of 234 to 1,169 ng/mL. The binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. ZYROLBINE binding was not altered in the presence of cisplatin, 5-fluorouracil or doxorubicin.

INDICATIONS
ZYROLBINE is indicated as a single agent or in combination with cisplatin for the first-line treatment of ambulatory patients with unresectable, advanced nonsmall cell lung cancer (NSCLC). In patients with Stage IV NSCLC, ZYROLBINE is indicated as a single agent or in combination with cisplatin. In Stage III NSCLC, ZYROLBINE is indicated in combination with cisplatin.

DOSAGE & ADMINISTRATION:

Dose Modifications for Hepatic Insufficiency
ZYROLBINE should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with ZYROLBINE, the dose should be adjusted for total bilirubin according to Table 6.

Dose Modification for Concurrent Hematologic Toxicity and Hepatic Insufficiency
In patients with both hematologic toxicity and hepatic insufficiency, the lower of the doses based on the corresponding starting dose of ZYROLBINE determined from Table 5 and Table 6 should be administered.

Dose Modifications for Renal Insufficiency
No dose adjustments for ZYROLBINE are required for renal insufficiency. Appropriate dose reductions for cisplatin should be made when ZYROLBINE is used in combination.

Dose Modifications for Neurotoxicity: If Grade ≥2 neurotoxicity develops, ZYROLBINE should be discontinued.

Administration Precautions
Caution – ZYROLBINE must be administered intravenously. It is extremely important that the intravenous needle or catheter be properly positioned before any ZYROLBINE is injected. Leakage into surrounding tissue during intravenous administration of ZYROLBINE may cause considerable irritation, local tissue necrosis, and/or thrombophlebitis. If extravasation occurs, the injection should be discontinued immediately, and any remaining portion of the dose should then be introduced into another vein. Since there are no established guidelines for the treatment of extravasation injuries with ZYROLBINE, institutional guidelines may be used. The ONS Chemotherapy Guidelines provide additional recommendations for the prevention of extravasation injuries.1

As with other toxic compounds, caution should be exercised in handling and preparing the solution of ZYROLBINE. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If the solution of ZYROLBINE contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water. Severe irritation of the eye has been reported with accidental contamination of the eye with another vinca alkaloid. If this happens with ZYROLBINE, the eye should be flushed with water immediately and thoroughly.

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Preparation for Administration
ZYROLBINE Tartrate Injection must be diluted in either a syringe or IV bag using one of the recommended solutions. The diluted ZYROLBINE should be administered over 6 to 10 minutes into the side port of a free-flowing IV closest to the IV bag followed by flushing with at least 75 to 125 mL of one of the solutions. Diluted ZYROLBINE may be used for up to 24 hours under normal room light when stored in polypropylene syringes or polyvinyl chloride bags at 5° to 30°C (41° to 86°F).

Syringe: The calculated dose of ZYROLBINE should be diluted to a concentration between 1.5 and 3.0 mg/mL. The following solutions may be used for dilution:

5% Dextrose Injection
0.9% Sodium Chloride Injection

IV Bag: The calculated dose of ZYROLBINE should be diluted to a concentration between 0.5 and 2 mg/mL. The following solutions may be used for dilution:
5% Dextrose Injection
0.9% Sodium Chloride Injection
0.45% Sodium Chloride Injection
5% Dextrose and 0.45% Sodium Chloride Injection
Ringer's Injection
Lactated Ringer's Injection

Stability
Unopened vials of ZYROLBINE are stable until the date indicated on the package when stored under refrigeration at 2° to 8°C (36° to 46°F) and protected from light in the carton. Unopened vials of ZYROLBINE are stable at temperatures up to 25°C (77°F) for up to 72 hours. This product should not be frozen.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If particulate matter is seen, ZYROLBINE should not be administered.

WARNINGS
ZYROLBINE should be administered in carefully adjusted doses by or under the supervision of a physician experienced in the use of cancer chemotherapeutic agents.

Patients treated with ZYROLBINE should be frequently monitored for myelosuppression both during and after therapy. Granulocytopenia is dose-limiting. Granulocyte nadirs occur between 7 and 10 days after dosing with granulocyte count recovery usually within the following 7 to 14 days. Complete blood counts with differentials should be performed and results reviewed prior to administering each dose of ZYROLBINE. ZYROLBINE should not be administered to patients with granulocyte counts <1000 cells/mm3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection and/or fever. See DOSAGE AND ADMINISTRATION for recommended dose adjustments for granulocytopenia.

Acute shortness of breath and severe bronchospasm have been reported infrequently, following the administration of ZYROLBINE and other vinca alkaloids, most commonly when the vinca alkaloid was used in combination with mitomycin. These adverse events may require treatment with supplemental oxygen, bronchodilators, and/or corticosteroids, particularly when there is pre-existing pulmonary dysfunction.

Reported cases of interstitial pulmonary changes and acute respiratory distress syndrome (ARDS), most of which were fatal, occurred in patients treated with single-agent ZYROLBINE. The mean time to onset of these symptoms after ZYROLBINE administration was 1 week (range 3 to 8 days). Patients with alterations in their baseline pulmonary symptoms or with new onset of dyspnea, cough, hypoxia, or other symptoms should be evaluated promptly.

ZYROLBINE has been reported to cause severe constipation (e.g., Grade 3-4), paralytic ileus, intestinal obstruction, necrosis, and/or perforation. Some events have been fatal.

PRECAUTIONS:

Pregnancy
ZYROLBINE may cause fetal harm if administered to a pregnant woman. A single dose of ZYROLBINE has been shown to be embryo- and/or fetotoxic in mice and rabbits at doses of 9 mg/m2 and 5.5 mg/m2, respectively (one third and one sixth the human dose). At nonmaternotoxic doses, fetal weight was reduced and ossification was delayed. There are no studies in pregnant women. If ZYROLBINE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with ZYROLBINE.

Adverse Reactions:

Hematological Toxicity:
The DL T is myelosuppression consisting of granulocytopenia, anemia, and thrombocytopenia. Granulocytopenia occurs in two-thirds of patients. The onset is day 7-14 and he recovery by day 14-24. The proportion of affected cycles is relatively low at 9.1% and recovery is rapid. Although the incidence of the condition is high. It is manageable with dose modifications and severe complications are uncommon. Only 7% of the patients require hospitalization for neutropenic fever or documented infection, an indication that the duration of granulocytopenia is not extreme. The incidence of neutropenia and leukopenia decline during subsequent weeks of treatment (reversible and non-cumulative). Severe marrow toxicity is uncommon. Anemia is frequent but moderate. Thrombotic events such as pulmonary embolism and deep venous thrombosis have been reported with Vinorelbine therapy. These events primally occurred in seriously ill and debilitated patients with known predisposing factor for these conditions.

Non-hematological toxicities:
These includes nausea and vomiting (usually controlled with standard antimentics) constipation, peripheral neuropathy, weakness, alopecia and pain at the injection site.

Gastrointestinal :

Mild to moderate nausea (34% of patients). Due to low incidence of severe nausea & vomiting with Vinorelbine, the use of serotonin antagonists is generally not required. Constipation (29%) with rate case of paralytic ileus have been described. Intestinal obstruction, necrosis and/or perforation have also been reported.

Neurotoxicity:
Low grade peripheral neuropathy manifested by parenthesis and muscle weakness, may occur (20%) & loss of deep tendon reflexes (<5% of patients). Weakness in lower limbs may be observed after prolonged treatment Neurotoxity appears to be reversible after discontinuation.

Pulmonary :
Dyspnea, cough and bronchospasm associated with interstitial infiltrates may occur. These reactions occur usually a few minutes following injection or several hours later. Pulmonary edema, acute respiratory failure and ARDS have also been reported.

Alopecia : Moderate (in 35% of patients)
Skin : Continuous intravenous infusion have been associated in 16% cases with grade 3-4 reactions like pain on injection, venous pain & thrombophlebitis. Similar reactions have been noted in 5-10% cases with short infusion (20mon), Hand foot syndrome has also been reported.

Musculo-skeletal:
Myalgia, muscle weakness and law pain are associated in 5% p[atients. They are considered secondary to neurotoxicity.

Extravasation : Can lead to an injection site reaction including pain, skin ulcer and tissue necrosis,. Chemical phlebitis along the vein proximal to the injection site is reported (10%). Development of ulcers following Vinorelbine extravasation may be delayed. If extravasation occurs, treatment with warm compressors and hyaluronidase is effective in preventing ulcer formation. The infusion should be stopped and completed vial another vein, preferably in another limb. Skin discoloration along the vein is reported in one-third of patients.

Others : Electrolyte arthormalities, including hyponatremia with or without the syndrome of inappropriate ADH, SIADH secretion, have been reported (<1%) in seriously ill and debilitated patients.
Hemarrhagic cystitis, elevation of SGPT and alkaline phosphatase have also been reported though rare. Allergic type of reactions have also been reported (>2%).

Drug Interactions:
Acute pulmonary reactions have been reported with ZYROLBINE and other anticancer vinca alkaloids used in conjunction with mitomycin. Although the pharmacokinetics of ZYROLBINE are not influenced by the concurrent administration of cisplatin, the incidence of granulocytopenia with ZYROLBINE used in combination with cisplatin is significantly higher than with single-agent ZYROLBINE. Patients who receive ZYROLBINE and paclitaxel, either concomitantly or sequentially, should be monitored for signs and symptoms of neuropathy. Administration of ZYROLBINE to patients with prior or concomitant radiation therapy may result in radio sensitizing effects. Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of ZYROLBINE tartrate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects.

OVERDOSAGE:
No known antidote for overdoses of Vinorelbine. Overdose involving quantities up to 10times the recommended dose (30mg/m2) have been reported. The toxicities include severe granulovytopenia with a risk of infection, paralytic ileus, stomatitis, and esophagitis. Bone marrow aplasis, sepsis, and paresis have also been reported. It overdosage occur, general supportive measures together with appropriate blood transfusions, growth factore, and antibiotics should be instituted as deemed necessary.

CONTRAINDICATIONS

- In patients with pretreatment granulocyte counts

STORAGE:

Store between 2° to 8°C. Protect from light. DO NOT FREEZE.

PRESENTATION:

Zyrolbine (Vinorelbine Injection I>P.) is available as injection containing Vinorelbine Tartrate I.P. equivalent to Vinorelbine 10 mg/1 mL and 50 mg/5 mL.

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
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