moderate heat to the area of leakage help disperse the drug and are thought to minimize discomfort and the possibility of cellulites.

The drug is to be administered intravenously at weekly intervals. In the presence of leukopenia, or a complicating infection administration of the next dose of Cytocristin warrants careful consideration.

*Adults*
1.4 mg/m$^2$
*Children*
2 mg/m$^2$
*Children weighing 10 kg or less*

The starting dose should be 0.05mg/kg once a week.

*In impaired hepatic function*
Cytocristin should not be given to patients while they are receiving radiation therapy through ports that include the liver.

In patients having a direct serum bilirubin value above 3mg/100ml the dose is reduced by 50 percent. Subsequent doses may be increased depending on tolerance to the initial treatment.

*In impaired renal failure*
No dosage adjustment is necessary in patients with renal failure.

*Use in Elderly*
No specific dosage regimen is required for use in elderly.

**Symptoms and treatment of overdose**
Side-effects are dose related. Therefore following administration of more than the recommended dose, patients can be expected to experience exaggerated side effects. Supportive care should include :

a. Prevention of side effects that result from the syndrome of inappropriate secretion of anti-diuretic hormone;
b. Administration of anticonvulsants;
c. Use of enemas or cathartics to prevent paralytic ileus
d. Monitoring the patient's cardiovascular system and daily blood counts for guidance in transfusion requirements.
e. daily blood counts for guidance in transfusion requirements.

Animal studies indicate that folinic acid is effective in the treatment of overdosage. A suggested schedule is to administer 100mg of folinic acid intravenously every 3 hours for 24 hours and then every 6 hours for atleast 48 hours.

***Storage***
Store at 2 to 8°C in a refrigerator.Do not freeze. Protected from light.

**Packing/Pack Size**
Vial containing 1ml.

**Shelf Life**
18 months

**Registration holder in Malaysia**
**CIPLA MALAYSIA SDN BHD**
Suite 1101, Amcorp Tower,
Amcorp Trade Centre 18,
Persiaran Barat
46050 Petaling Jaya
Selangor, Malaysia

**NAME OF MANUFACTURER :**
**CIPLA LIMITED.**
Verna Industrial Estate
403722 Goa INDIA

**Date of Revision: February 2015**

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*For the use of a Cancer Specialist or Hospital.*

# **Cytocristin Aqueous** Injection

**Composition**

Each ml contains
Vincristine sulfate USP ..... 1mg
Mannitol BP ..... 100mg
Preservatives
Methyl paraben BP ..... 0.13%w/v
Propyl paraben BP ..... 0.02%w/v
In water for injection BP ..... q.s.

Acetic acid USP and Sodium Acetate USP have been added to adjust pH from 3.5 to 5.5.

**Description**

Sealed colourless vials containing a clear, colourless solution.

**Pharmacology (Pharmacodynamics & Pharmacokinetics)**
***Pharmacodynamics***
Although the mechanism of action has not been fully elucidated vincristine and other vinca alkaloids exert their cytotoxic effects by binding to tubulin, the protein subunit of the microtubules that form the mitotic spindle. The formation of vincristine-tubulin complexes prevents the polymerization of the tubulin subunits into microtubules and induces depolymerization of microtubules resulting in inhibition of microtubule assembly and cellular metaphase arrest. In high concentrations, the drug also exerts complex effects on nucleic acid and protein synthesis. Vincristine exerts some immunosuppressive activity.

***Pharmacokinetics***
**Absorption**
Vincristine sulfate is unpredictably absorbed from the GI tract. Following rapid IV injection of a 2mg dose of vincristine in patients with normal renal and hepatic function, peak serum drug concentrations of approximately 0.19-0.89µM occur immediately and the drug is rapidly cleared from serum.The area under the serum vincristine concentration-time curve has been shown to be increased following continuous IV infusion compared with rapid IV injection of the drug when comparable doses are administered.

**Distribution**
Distribution of vincristine and its metabolites into human body tissues and fluids has not been fully characterized, but the drug is rapidly and apparently widely distributed following IV administration. Drug that is distributed into tissues is tightly but reversibly bound. Vincristine and its metabolites are rapidly and extensively distributed into bile, with peak biliary concentrations occurring within 2-4 hours after rapid IV injection of the drug. Vincristine and its metabolites cross the blood-brain barrier poorly following rapid IV injection and generally do not appear in the CSF in cytotoxic concentrations. It is not known whether vincristine and its metabolites are distributed into milk.

**Elimination**
Following rapid IV injection of vincristine, serum concentrations of the drug appear to decline in a triphasic manner. The terminal elimination half-life of vincristine has ranged from 10.5-155 hours.

The metabolic fate of vincristine has not been clearly determined; the drug appears to be extensively metabolized, probably in the liver by the cytochrome P-450 microsomal enzyme system, including CYP3A, but the extent of metabolism is not clear since the drug also apparently undergoes decomposition in vivo. In patients with hepatic impairment metabolism of vincristine may be decreased. Vincristine and its metabolites are excreted principally in feces via biliary elimination. The effects of hepatic impairment on the elimination of vincristine and its metabolites have not been evaluated, but individuals with decreased hepatic function may have impaired elimination.

**Indications**
Cytocristin is indicated in the treatment of acute leukemia, and as combination therapy with other oncolytic agents in the treatment of Hodgkin's disease, non-hodgkin's malignant lymphoma's (lymphocytic, mixed cell, histiocytic, undifferentiated, nodular and diffuse types), rhabdomyosarcoma, neuroblastoma and Wilms' tumour.

**Contraindications**
Demyelinating form of Charcoat-Marie Tooth Syndrome.

**Side Effects**
In general adverse reactions to vincristine are dose-related and reversible. The most common adverse reaction is hair loss, the most troublesome adverse reactions are neuromuscular in origin. When single weekly doses of the drug are employed, the adverse reactions of leukopenia, neurotic pain and constipation occur but are usually of short duration. When the dosage is reduced the reactions may lessen or disappear. The severity of such reactions seems to increase when the calculated amount of drug is given in divided doses. Other adverse reactions, such as hair loss, sensory loss, paresthesia, difficulty in walking, slapping gait, loss of deep tendon reflexes and muscle wasting may persist for at least as long as therapy is continued. Almost all symptoms usually disappear by about the sixth week after discontinuance of therapy. Some neuromuscular difficulties may persist for prolonged periods in some patients. Regrowth of hair may occur while maintenance therapy continues. The following adverse reactions have been reported :

Hypersensitivity or allergic type reactions : Anaphylaxis, rash.

Gastrointestinal : Constipation, abdominal cramps, nausea, weight loss, vomiting, oral ulceration, diarrhoea, paralytic ileus, intestinal necrosis and/or perforation and anorexia have occurred. All cases have responded to high enemas and laxatives.

Genito-urinary : Polyuria, dysuria, urine retention due to bladder atony.

Cardiovascular : Hypertension and hypotension.

Haematologic : Serious bone-marrow depression is usually not a major dose limiting event. However anaemia, leukopenia and thrombocytopenia have been reported.

Ophthalmic : Optic atropy with blindness, transient cortical blindness, diplopia, photophobia.

Endocrine : Rare cases of a syndrome attributed to inappropriate antidiuretic hormone secretion have been observed. With fluid deprivation improvement occurs in the hypoatremia and in the renal loss of sodium.

Neurologic : Loss of deep tendon reflexes, foot drop ataxia and paralysis have been reported with continued administration. Myalgias have occurred. Severe pain in the jaw, pharynx, parotid gland, bone, back and limb.

**Precautions & warnings**
Acute uric acid nephropathy may occur.
CNS leukemia has occurred in patients undergoing otherwise successful therapy with vincristine. If CNS leukemia is diagnosed additional agents may be required since this drug does not adequately cross the blood-brain barrier.

Particular attention should be given to dosage and neurological side effects if administered to patients with pre-existing neuromuscular disease.

Eye contamination should be avoided with concentrations used clinically. If accidental contamination occurs severe irritation may result. Eyes should be washed immediately and thoroughly.

**PREGNANCY**
There are no adequate and well-controlled studies in pregnant women. Vincristine can cause fetal harm when administered to a pregnant woman. If the drug is used during pregnancy or if the patient receiving it, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

**NURSING MOTHERS**
It is not known whether the drug is secreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

**IN IMPAIRED RENAL FUNCTION**
See Dosage and Administration

**DRUG INTERACTIONS**
L-asparaginase : Administering L-asparaginase before vincristine may reduce the hepatic clearance of the drug. Therefore when used in combination, vincristine should be given 12-24 hours before L-asparaginase administration to minimise toxicity.

Mitomycin C: Acute pulmonary reactions might occur on concomitant administration of mitomycin C.

Phenytoin : The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine sulfate has been reported to reduce blood levels of the

anticonvulsant and to increase seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vincristine sulfate to this interaction is not certain. The interaction may result from reduced absorption of phenytoin and an increase in the rate of its metabolism and elimination.

Solvents : Cytocristin should not be diluted in solutions that raise or lower the pH outside the range of 3.5 to 5.5; it should not be mixed with anything other than normal saline.

Itraconazole : Concurrent administration of Vincristine Sulfate with Itraconazole (a known inhibitor of the metabolic pathway) has been reported to cause an earlier onset and/or an increased severity of neuromuscular side effects. This interaction is presumed to be related to Inhibition of the metabolism of vincristine.

**Dosage & Administration**
**This preparation is for intravenous use only. Intrathecal use of the drug could be fatal.**
*Precautions for administration*
Extreme care must be taken in calculating and administering the dose of Cytocristin, since overdosage may have a very serious or fatal outcome.

The solution should be withdrawn into an accurate dry syringe. No extra fluid should be added to the vial in an attempt to empty it completely.

The drug may be injected either directly into a vein or into the tubing of a running intravenous infusion. Injection of Cytocristin should be accomplished within one minute.It is extremely important that the intravenous needle or catheter may be properly positioned before Cytocristin is injected. Leakage into surrounding tissue during intravenous administration of Cytocristin may cause considerable irritation. If extravasation occurs the injection should be discontinued immediately and the remaining portion of the dose should be discontinued immediately and the remaining portion of the dose should then be introduced into another vein. Local injection of hyaluronidase and the application of

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## PACKAGING DEVELOPMENT

| | | | |
|---|---|---|---|
| **Product Name: Cytocristin** | **Material No.** | **Item:** Leaflet | **Date: 08-09-15** |
| **Co-ordinator: Swati** | **Artist: Devendra** | **Software: I**llustrator CC | |
| **Fonts:** | | | |
| **Colours:** BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA) ■ Black | | | |
| **INK:** Oil based Ink from DIC OR MICRO | | | |
| **Spectro-Densitometer Delta-E reading (△E) for colour:** NOT MORE THAN dE2.5 | | **Glossmeter reading (for white surface):** NOT LESS THAN 80 % | |
| **Supersedes / Reference:** 799VZ | | **Screen : # __** | |
| **Links:** | | | |
| **Pharmacode/2D Code:** | | **Design:** Folded | |
| **Material:** 54 GSM Maplitho Paper | | **Varnish:** | |
| **Actual Size: 110 x 180 mm** | | **Size after folding: 110 x 18 mm** | |
| **Grain Direction :** Parallel to length | | | |
| **Reference / Instructions / Remark / Braille Text Embossing:** | | | |
| **Artwork Print Size:** ☐ **actual** ☐ **scaled** | | | |
| **Path:PC:D:Devendra\Swati\Cipla Malaysia\Cytocristin** | | | |

| Checked by | Artist | Cordinator | Section Head | File Copied by | file loaded in BCT HO |
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| Pharma Code | ☐ | ☐ | | | |
| 2D Code | ☐ | ☐ | | | |
| Barcode Code | ☐ | ☐ | | | |
| Artwork | ☐ | ☐ | | | |
| Spell check | ☐ | ☐ | | Date: | |

**NOTE TO THE PRINTER :**

- Return approved artwork alongwith the proof.
- The proof must be verified against the approved hardcopy, should be certified and signed by an authorised QA person. The unsigned proof will not be accepted.
- Colour scheme must be as approved by packaging development co-ordinator.
- Any deviation must be brought to the notice of packaging development co-ordinator immediately.
- For any clarification, please contact packaging development co-ordinator immediately.