

VINCRIStINE

(Antineoplastic Agent, Vinca Alkaloid)

Revision Date: Feb 03

COMMERCIAL PRODUCT DESCRIPTION

Brand Name: Oncovin® Vials with 1mg/1mL, 2mg/2mL, 5mg/5mL
 Generic products available Prefilled syringes with 2mg/2mL

MECHANISM OF ACTION

Vincristine binds to tubulin, inhibiting microtubule formation. The resulting metaphase arrest causes disruption of the mitotic spindle. It may also interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization. It is specific for the M and S phase of the cell cycle. It may also interfere with nucleic acid and protein synthesis by blocking glutamic acid utilization.

PHARMACOKINETICS

Oral Absorption

poor oral absorption

Distribution

rapid and extensive tissue binding; enters breast-milk
 cross blood brain barrier? CSF: plasma ratio 5%,
 rapidly cleared from the bloodstream

Vd 8.4 L/kg, 163-165 L/m² PPB ~75%

Metabolism

metabolized in liver, not fully characterized
 metabolite(s): active, inactive- no information

Excretion

disposition described by a three compartment model;
 excreted into bile (80%) and feces (~30% within 24
 Hours, 70% within 72 hours, 40-50% as metabolites),
 renal (10-20%)

Urine: 12% within 72 hours, 50% as metabolites;
 children: 37% within 72 hours; <1% as unchanged
 drug

t_{1/2} α - 5 minutes t_{1/2} β - 2.3 hours
 t_{1/2} γ - 23-85 hours; 25.5 hours (children)

Cl 146 mL/min/1.73 m²

ROUTES

direct IV (preferred)
 intermittent IV (in 50-250 mL over 0.25-2 hours,
 Venous Access Device preferred)
 continuous IV (via Venous Access Device)

ADMINISTRATION

- Quick push through sidearm of free flowing IV (5% Dextrose, Normal Saline); Inject over at least 1 minute (*administering nurse should be certified to administer IV push chemotherapy agents*)
- May be given by direct IV push, followed by a Normal Saline flush, if no IV line has been set up
- Mix in 50mL minibag (Normal Saline, 5% Dextrose); Infuse over 15 minutes
- Mix in 1000mL bag (Normal Saline, 5% Dextrose); usually admixed with doxorubicin as a continuous infusion for 4 days (96 hours) at a dose of 0.4 mg/day.
- **Continuous infusion** using ambulatory infusion pump. Infuse through central venous access device or PICC line, if available
- Peripheral administration of continuous infusions of vesicants are not recommended.

IV COMPATIBILITY

normal saline, dextrose 5%

SIDE EFFECTS

* may be life-threatening

side effects in **bold, italic** type are common

IMMEDIATE ONSET (hours to days)

nerve problems (jaw pain, peripheral neuropathy)
 nausea and vomiting (uncommon, usually mild)
 seizures in children, hallucinations (central neurotoxicity)
 increased uric acid levels (hyperuricemia)
 fever in children

* pulmonary toxicity (acute shortness of breath, bronchospasm)

EARLY ONSET (continued)

constipation (may be severe, autonomic neuropathy)
 paralytic ileus (more common in children, autonomic neuropathy)
 bladder problems (urinary retention, bladder atony, autonomic neuropathy)
 progressive dyspnea

* low WBC (usually mild, myelosuppression, nadir 4-9 days, recovery 7-21 days)

eye problems (cranial nerve neuropathy)
 SIADH (rare, hyponatremia, central neurotoxicity)

EARLY ONSET (days to weeks)

hair loss (alopecia), 50%, usually mild)
nerve problems (peripheral, cranial nerve and autonomic neuropathy)

DELAYED/LATE ONSET

eye problems (cranial nerve neuropathy)

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VINCRIStINE (continued)

INDICATIONS AND OTHER USES

- Acute lymphocytic leukemia
- Ewing's sarcoma
- Hodgkin's disease
- Lung cancer, small cell
- Non-Hodgkin's lymphoma
- Rhabdomyosarcoma
- Wilm's tumour
- Brain tumours
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Malignant melanoma
- Neuroblastoma
- Osteogenic sarcoma
- Soft tissue sarcoma

OTHER ONCOLOGY USES (Not Approved)

Chronic lymphocytic leukemia
Chronic myelogenous leukemia
Hepatoblastoma in children
Kaposi's sarcoma
Multiple myeloma
Testicular cancer

DOSING

Intravenous:

- q1w: 1.0-1.4 mg/m²
- q2w: 1-2 mg
- q4w: 0.4 mg/day x 4 days as intermittent or continuous infusion
- q4w: 0.25-1 mg/m²/day x 5 days as continuous infusion

Pediatric

Intravenous:

- q1w: 1-2 mg/m² (maximum single dose 2 mg)
- q1w: 0.03-0.05 mg/kg for infants <1 m²

Other dosing may be indicated in specific regimens

CONTRAINDICATIONS

Hypersensitivity to vincristine, or other vinca alkaloids
 pregnancy and breast feeding
 demyelinating form of Charcot-Marie-Tooth Syndrome
 Cytochrome P450 enzyme substrates

CLINICAL MONITORING

RECOMMENDED CRITERIA

- **Complete blood count including differential, platelets and hemoglobin (CBC)** before each cycle of treatment
- **Neurologic toxicity** ratings (Sensory, Constipation) at each visit

SENSORY

0. No change
1. Mild paraesthesia; no deep tendon reflex
2. Mild/moderate sensory loss; moderate paraesthesia
3. Sensory loss interferes with function

CONSTIPATION

0. No change
1. Mild
2. Moderate
3. Severe
4. Ileus >96 hours

Rated At Each Clinic Visit

SUGGESTED CRITERIA

- **Serum electrolytes** and **serum uric acid levels** (if symptomatic of hyperuricemia/gout)
- Baseline **liver function tests** (if liver failure suspected) [serum alkaline phosphatase, GGT, ALT, AST & Bilirubin levels (serum proteins may be added if indicated)]
- Local Site Toxicity ratings, if incident of phlebitis

LOCAL SITE TOXICITY

0. None
1. Pain
2. Pain & inflammation; phlebitis
3. Ulceration
4. Plastic surgery

Upon Patient Complaint Or Clinical Event

EXTRAVASATION HAZARD

VESICANT (tissue damage on extravasation)
 Management- stop IV, aspirate, elevate limb, warm intermittent compresses
 Follow Extravasation Guidelines
See Appendix 4D

ANTIEMETIC RISK

LOW RISK (Less than 10% of patients)

- No routine antiemetic pre-chemotherapy or post-chemotherapy

See Nausea & Vomiting Guidelines for more detail

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VINCRIStINE (continued)

PHARMACEUTICAL CONSIDERATIONS

Vincristine is lethal if given intrathecally. No successful antidotes have been described. The Compendium of Pharmaceuticals and Specialties (CPS) and the United States Pharmacopeia (USP) requires that vincristine be dispensed in an overwrap bearing the statements "Do not remove covering until moment of injection. Fatal if given intrathecally. For intravenous use only."

Injection

1 mg/mL solution (1 mL, 2 mL and 5 mL vials); also contains mannitol. Some products contain methyl- and propylparaben as preservatives and acetic acid/sodium acetate buffer. Store in refrigerator, protected from light; do not freeze. One reference states that vincristine vials are stable at room temperature 3 days and 30 days, for two different manufacturers respectively.

Diluted solution for infusion

May be further diluted with D5W or NS. DBL states that diluted solutions should be used within 6 hours if stored at room temperature or 24 hours when refrigerated and protected from light. Trissel reports no loss of vincristine in D5W after 24 hours storage at room temperature in glass and PVC containers. Admixtures of doxorubicin (1.4 mg/mL) plus vincristine (0.033 mg/mL) in NS or sodium chloride 0.45 % and dextrose 2.5% injection are stable at least 4 days in PVC containers and Pharmacia cassettes at temperature 37°C. Variable losses (up to 12%) to some filters have been reported, although filtration through Abbott IVEX in-line filters, which are specially treated with a proprietary agent, resulted in losses of only 1%. Some mixtures with cytarabine, fluorouracil and methotrexate are reported stable in D5W for at least 8 hours at room temperature; some mixtures with doxorubicin in NS or D5W are stable for at least 24 hours. Compatible with ondansetron. It is recommended that vincristine not be mixed with other drugs. Incompatible (immediate precipitation) with furosemide.

DOSE ADJUSTMENT CRITERIA

Hepatic dysfunction

50% if Bili= 25-50µmol/L or AST= 60-180IU/L;

25% if Bili > 50µmol/L or AST > 180IU/L

(Recommended action)

Dose Capping

- Some regimens specify that the dose be capped at 2mg/dose, but others do not require capping. Doses >3mg should be confirmed with the oncologist or hematologist

ADMINISTRATIVE INFORMATION

CCNS Provincial Formulary Status- Basic Level

CDHA Formulary Status Formulary

Pharmacare Formulary Status Formulary (red)

SIGNIFICANT INTERACTIONS

anticonvulsant drugs, asparaginase, carbamazepine, cyclosporin, digoxin, filgrastim, irradiation, isoniazid, itraconazole, metronidazole, mitomycin, nifedipine, phenytoin, steroid hormones, verapamil, other antineoplastic agents

Cytochrome P450 3A Substrate:

See **Appendix 3F** for further details