09-J1000-03

Original Effective Date: 05/15/09

Reviewed: 12/12/12

Revised: 11/01/15

Subject: Vinorelbine Tartrate (Navelbine®) IV

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Vinorelbine 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 vinorelbine. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Like other vinca alkaloids, vinorelbine may also interfere with: 1) amino acid, cyclic AMP, and glutathione metabolism, 2) calmodulin-dependent Ca++-transport ATPase activity, 3) cellular respiration, and 4) nucleic acid and lipid biosynthesis. In intact tectal plates from mouse embryos, vinorelbine, vincristine, and vinblastine inhibited mitotic microtubule formation at the same concentration (2 mcM), inducing a blockade of cells at metaphase. Vincristine produced depolymerization of axonal microtubules at 5 mcM, but vinblastine and vinorelbine did not have this effect until concentrations of 30 mcM and 40 mcM, respectively. These data suggest relative selectivity of vinorelbine for mitotic microtubules.

POSITION STATEMENT:

Vinorelbine Tartrate IV **meets the definition of medical necessity** when administered for the following:

- Advanced Kaposi's Sarcoma
- Breast Cancer
- Desmoid Tumor

- Hodgkin's Lymphoma
- Non-Hodgkin's Lymphoma
- Non-Small Cell Lung Cancer (NSCLC)
- Ovarian Cancer
- Small Cell Lung Cancer (SCLC)
- Soft Tissue Sarcoma
- Malignant Pleural Mesothelioma**; AND**
- dosage does not exceed 30 mg/meter squared every 7 days.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Adults

Non-small cell lung cancer: Single-agent therapy is 30 mg/m2 administered IV over 6 to 10 minutes once weekly. In controlled trials, single-agent vinorelbine was given weekly until progression or dose-limiting toxicity.

Combination therapy with cisplatin: Usual dosage is25 mg/m2 administered IV once weekly in combination with cisplatin 100 mg/m2 every 4 weeks.

Alternative dosage: 30 mg/m2 administered IV once weekly in combination with cisplatin 120 mg/m2, given on days 1 and 29, then every 6 weeks.

Extravasation: Administration of vinorelbine tartrate may result in extravasation causing local tissue necrosis or thrombophlebitis. If signs or symptoms of extravasation occur, stop the infusion immediately. If possible, withdraw 3 to 5 mL of blood to remove some of the drug. Remove the infusion needle. Administer hyaluronidase 150 units/mL solution within the first few minutes to 1 hour after extravasation. Cleanse the area with povidone-iodine. Reconstitute 1 mL vial of hyaluronidase. (Note: Some products do not require dilution.) Inject locally, subcutaneously or intradermally, using a 25-gauge needle or smaller. The dose is 150 units (1 mL) given as 5 injections (0.2 mL each). Application of warm compresses to the area for 15 minutes every 6 hours for 48 hours may be useful. Delineate the infiltrated area on the patient's skin with a felt-tip marker. Elevate for 48 hours above heart level using a sling or stockinette dressing with an observation window cut in the dressing. Avoid pressure or friction. Do not rub the area. Observe for signs of increased erythema, pain, or skin necrosis. If increased symptoms occur, consult a plastic surgeon. Ensure that no medication is given distally to extravasation site. After 48 hours, encourage the patient to use the extremity normally to promote full range of motion.

Children

Safety and effectiveness in children have not been established. No pediatric dosing information is available.

PRECAUTIONS:

WARNING
Vinorelbine tartrate injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. This product is for IV use only. Intrathecal administration of other vinca alkaloids has resulted in death. Syringes containing this product should be labeled "Warning – for IV use only. Fatal if given intrathecally." Severe granulocytopenia resulting in increased susceptibility to infection may occur. Granulocyte counts should be greater than or equal to 1000 cells/mm3 prior to the administration of vinorelbine tartrate. The dosage should be adjusted according to complete blood counts with differentials obtained on the day of treatment. **Caution:** It is extremely important that the intravenous needle or catheter be properly positioned before vinorelbine tartrate is injected. Administration of vinorelbine tartrate may result in extravasation causing local tissue necrosis or thrombophlebitis.

Contraindication: Pretreatment granulocyte counts less than 1000 cells/mm^3.

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

Myelosuppression: Patients treated with vinorelbine tartrate 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 vinorelbine tartrate. Vinorelbine tartrate should not be administered to patients with granulocyte counts less than 1000 cells/mm3. Patients developing severe granulocytopenia should be monitored carefully for evidence of infection or fever. Patients with a granulocyte count of greater than or equal to 1500 cells/mm3 on treatment days should receive 100% starting dose of vinorelbine. Patients with a granulocyte count of 1000 to 1499 cells/mm3 on treatment days should receive 50% starting dose of vinorelbine. Patients with a granulocyte count less than 1000 cells/mm3 on treatment days should not receive vinorelbine; repeat the granulocyte count in 1 week and if 3 consecutive weekly doses are held because of the granulocyte less than 1000 cells/mm3, discontinue vinorelbine.

Pulmonary toxicity: Reported cases of interstitial pulmonary changes and acute respiratory distress syndrome (ARDS), most of which were fatal, occurred in patients treated with single-agent vinorelbine tartrate. The mean time to onset of these symptoms after vinorelbine 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.

Discontinuation: Most drug-related adverse events of vinorelbine tartrate are reversible. If severe adverse events occur, vinorelbine tartrate should be reduced in dosage or discontinued and appropriate corrective measures taken. Reinstitution of therapy with vinorelbine tartrate should be carried out with caution and alertness as to possible recurrence of toxicity.

Bone marrow: Vinorelbine tartrate should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy, or whose marrow function is recovering from the effects of previous chemotherapy.

Prior radiation therapy: Administration to patients with prior radiation therapy may result in radiation recall reactions.

Bronchospasm: Acute shortness of breath and severe bronchospasm have been reported infrequently, following the administration of vinorelbine tartrate 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, or corticosteroids, particularly when there is preexisting pulmonary dysfunction.

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GI: Vinorelbine tartrate has been reported to cause severe constipation (e.g., grade 3 to 4), paralytic ileus, intestinal obstruction, necrosis, or perforation. Some events have been fatal.

Eye contact: Care must be taken to avoid contamination of the eye with concentrations of vinorelbine tartrate used clinically. Severe irritation of the eye has been reported with accidental exposure to another vinca alkaloid. If exposure occurs, the eye should immediately be thoroughly flushed with water.

Hepatic function impairment: There is no evidence that the toxicity of vinorelbine tartrate is enhanced in patients with elevated liver enzymes. No data are available for patients with severe baseline cholestasis, but the liver plays an important role in the metabolism of vinorelbine tartrate. Because clinical experience in patients with severe liver disease is limited, caution should be exercised when administering vinorelbine tartrate to patients with severe hepatic injury or impairment.

Carcinogenesis: The carcinogenic potential of vinorelbine tartrate has not been studied.

Mutagenesis: Vinorelbine has been shown to affect chromosome number and possibly structure in vivo (polyploidy in bone marrow cells from Chinese hamsters and a positive micronucleus test in mice). It was not mutagenic in the Ames test and gave inconclusive results in the mouse lymphoma TK Locus assay. The significance of these or other short-term test results for human risk is unknown.

Fertility impairment: Vinorelbine did not affect fertility to a statistically significant extent when administered to rats on either a once-weekly (9 mg/m2, approximately one third the human dose) or alternate-day schedule (4.2 mg/m2, approximately one seventh the human dose) prior to and during mating. However, biweekly administration for 13 or 26 weeks in the rat at 2.1 and 7.2 mg/m2 (approximately one fifteenth and one fourth the human dose) resulted in decreased spermatogenesis and prostate/seminal vesicle secretion.

Children: Safety and effectiveness in pediatric patients have not been established. Data from a single-arm study in 46 patients with recurrent solid malignant tumors, including rhabdomyosarcoma/undifferentiated sarcoma, neuroblastoma, and CNS tumors, at doses similar to those used in adults, showed no meaningful clinical activity. Toxicities were similar to those reported in adults.

Elderly: Of the total number of patients in North American clinical studies of IV vinorelbine tartrate, approximately one third were 65 years of age or greater. No overall differences in effectiveness or safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Lab test abnormalities: Since dose-limiting clinical toxicity is the result of depression of the white blood cell count, it is imperative that complete blood counts with differentials be obtained and reviewed on the day of treatment prior to each dose of vinorelbine tartrate.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J9390	Vinorelbine tartrate, per 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

B20	Human immunodeficiency virus [HIV] disease
C33 – C34.92	Malignant neoplasm of trachea, bronchus and lung
C38.4	Malignant neoplasm of pleura
C46.0 – C46.9	Kaposi's sarcoma
C48.0 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.22	Malignant neoplasm of connective and soft tissue of head, face and neck, upper limb, including shoulder and lower limb, including hip
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified

C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C50.011 – C50.929	Malignant neoplasm of breast
C56.0 – C56.9	Malignant neoplasm of ovary
C57.00 – C57.4	Malignant neoplasm of fallopian tube, broad ligament, round ligament, parametrium and uterine adnexa, unspecified
C78.00 – C78.02	Secondary malignant neoplasm of lung
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
C79.51 – C79.52	Secondary malignant neoplasm of bone and bone barrow
C79.70 – C79.72	Secondary malignant neoplasm of adrenal gland
C7A.1	Malignant poorly differentiated neuroendocrine tumors
C81.00 – C81.99	Hodgkin lymphoma
C84.00 – C84.19	Mycosis fungoides and Sézary's disease
C84.93	Mature T/NK-cell lymphomas, unspecified, intra-abdominal lymph nodes
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue
Z80.49	Family history of malignant neoplasm of other genital organs
Z85.110	Personal history of malignant carcinoid tumor of bronchus and lung
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.3	Personal history of malignant neoplasm of breast
Z85.43	Personal history of malignant neoplasm of ovary
Z85.71	Personal history of Hodgkin lymphoma
Z85.831	Personal history of malignant neoplasm of soft tissue
Z85.89	Personal history of malignant neoplasm of other organs and systems

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) was found at the time of the last guideline revised date. The following Local Coverage Determination (LCD) was reviewed on the last guideline revised date: Vinorelbine Tartrate (Navelbine), (L34001) located at fcso.com.

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

Doxorubicin HCl Liposome (Doxil®) IV, 09-J0000-91

Carboplatin (Paraplatin®) IV, 09-J0000-93

Human EGFR Inhibitors (cetuximab; panitumumab) IV, 09-J0000-94

Docetaxel (Taxotere®) IV,. 09-J0000-95

Gemcitabine (Gemzar®), 09-J0000-96

Irinotecan HCl (Camptosar®) IV, 09-J0000-99

Oxaliplatin (Eloxatin®) IV, 09-J1000-00

OTHER:

None applicable.

REFERENCES:

1. Clinical Pharmacology. Copyright® 2011 Elsevier. Accessed 11/09/11.
2. DRUGDEX®. Accessed 11/09/11.
3. Facts & Comparisons® E Answers. Accessed 11/09/11.
4. Ingenix HCPCS Level II, Expert 2011.
5. Ingenix ICD-9-CM for Physicians-Volumes 1 & 2, Expert 2011.
6. Navelbine® Prescribing Information. Revised October 2007.
7. NCCN Drugs & Biologics Compendium™. Accessed 11/09/11.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/13.

GUIDELINE UPDATE INFORMATION:

05/15/09	New Medical Coverage Guideline.
10/15/09	Revision; consisting of clarifying dosage.

01/15/10	Revision; consisting of updating coding.
04/15/10	Revision; consisting of updating coding.
08/01/10	Revision; consisting of updating coding.
01/15/11	Review and revision; consisting of updating coding, related guidelines and references.
01/15/12	Review and revision to guideline; consisting of modifying position statement, updating dosage and administration, coding and references.
01/15/13	No Longer Review
12/15/13	Revision to guideline; consisting of adding new indication and updating coding.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.