FRINDOVYX®

(cyclophosphamide) injection

BILLING AND CODING GUIDE

If you have additional billing and coding questions, please call your Field Reimbursement Manager or AVYXASSIST™ at 866-939-8927. Our Patient Access Specialists are available to assist Monday through Friday, 8 AM to 8 PM ET.

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

AVYXA

TABLE OF CONTENTS

The contents herein provide general coverage, coding, and payment information about FRINDOVYX®. The information within this guide was obtained from third-party sources and is made available for reference only. It is not exhaustive, is subject to change, and does not constitute billing, coding, or legal advice. Healthcare professionals are responsible for determining which code(s, charge(s, or modifier(s, if any, appropriately reflect a service or diagnosis. It is the healthcare professional's responsibility to determine medical necessity and provide adequate documentation. AVYXA® does not guarantee coverage or payment. Payment and coverage vary by payer. Questions about coding, coverage, and payment may be directed to the applicable third-party payer, reimbursement specialist, and/or legal counsel.

CMS: Centers for Medicare & Medicaid Services; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; ICD: International Classification of Diseases; NDC: National Drug

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

Malignant Diseases

FRINDOVYX® is indicated for the treatment of adult and pediatric patients with:

- malignant lymphomas (Stages III and IV of the Ann Arbor staging system), Hodgkin's disease, lymphocytic lymphoma (nodular or diffuse), mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma
- multiple myeloma
- leukemias: chronic lymphocytic leukemia, chronic granulocytic leukemia (it is usually ineffective in acute blastic crisis), acute myelogenous and monocytic leukemia, acute lymphoblastic (stem-cell) leukemia (cyclophosphamide given during remission is effective in prolonging its duration)
- mycosis fungoides (advanced disease)
- neuroblastoma (disseminated disease)
- adenocarcinoma of the ovary
- retinoblastoma
- carcinoma of the breast

Cyclophosphamide, although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.

IMPORTANT SAFETY INFORMATION

DOSAGE AND ADMINISTRATION

Important Administration Instructions
During or immediately after the administration of **FRINDOVYX**, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. Therefore, FRINDOVYX® should be administered in the morning.

CONTRAINDICATIONS

Hypersensitivity

FRINDOVYX is contraindicated in patients who have a history of severe hypersensitivity reactions to cyclophosphamide, any of its metabolites, or to other components of the product. Anaphylactic reactions including death have been reported with cyclophosphamide. Cross-sensitivity with other alkylating agents can occur.

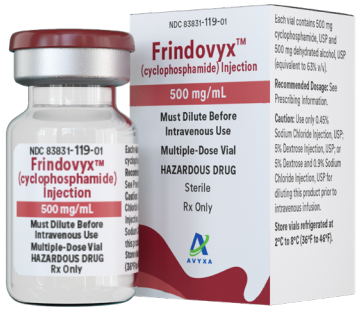
Urinary Outflow Obstruction

FRINDOVYX is contraindicated in patients with urinary outflow obstruction.

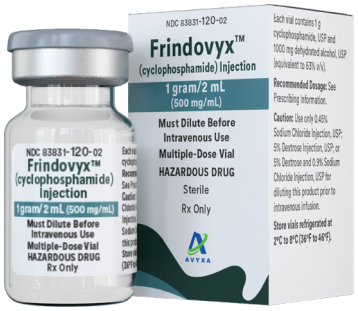
FRINDOVYX®
(cyclophosphamide) injection

Ordering Information

To order FRINDOVYX (cyclophosphamide) Injection, please contact one of these authorized specialty distributors and use the appropriate order number:



500 mg/mL
NDC: 83831-0119-01



1 gram/2 mL (500 mg/mL)
NDC: 83831-0120-02

2 gram/4 mL (500 mg/mL)
NDC: 83831-0121-04

Institutions/Hospitals	500 mg/mL	1 gram/2 mL	2 gram/4 mL
Cardinal Health Specialty	5970967	5970975	5970983
CENCORA - ASD Healthcare	10296622	10296595	10296609
McKesson Plasma & Biologics	3015880	3015906	3015914
Physician Offices	**500 mg/mL**	**1 gram/2 mL**	**2 gram/4 mL**
Cardinal Health Specialty	5970967	5970975	5970983
Oncology Supply	10296634	10296608	10296594
McKesson Specialty Health	5019686	5019687	5019688

Highlights[1]

UNIQUE J-CODE
J9072

- Supplied in multi-dose vials
- No reconstitution is required and ready to dilute solution
- Ready to add to direct intravenous injection with;
  - 0.9% Sodium Chloride Injection, USP
- Ready to add to the intravenous infusion solution with different options;
  - 0.9% Sodium Chloride Injection, USP
  - 0.45% Sodium Chloride Injection, USP
  - 5% Dextrose Injection, USP
  - 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- Partially used vials are stable for up to 28 days when stored refrigerated at 2°C to 8°C (36°F to 46°F)
- Not made with natural rubber.

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

AVYXASSIST™

Simplifying patient access, providing comprehensive support

AVYXASSIST can offer support to qualifying patients in need. The program provides the following services.*

- **Benefit verification**
- **Prior authorization requirements**
- **Appeals support**
- **Claims support**
- **Referrals to 501(c)(3) foundations**
- **Free product assistance**
- **Bridge supply**
- **Product replacement**
- **Copay assistance**

*For eligibility requirements, please contact a Patient Access Specialist. Terms and conditions apply.

To enroll, please choose one of the following options.

Call **866-939-8927**
Monday through Friday
8 AM to 8 PM ET

CALL NOW

Click on the link below to begin online enrollment

ENROLL NOW

Download, print, and fax a completed enrollment form to 833-852-3420

DOWNLOAD NOW

Commercially eligible patients prescribed **an AVYXA product** may pay as little as

$0 per dose*

Our dedicated AVYXASSIST Patient Access Specialists work collaboratively with you to explore tailored affordability solutions. AVYXA aims to facilitate financial accessibility for eligible patients in need.

ENROLL NOW

Copay Program Details for Eligible Patients

In some cases, the patient out-of-pocket cost for their AVYXA product could be as low as $0.*

- Up to $25,000 **per product** in annual benefits

*Please visit **avyxassist.com/copay-assistance-program** to see full Terms and Conditions.

Additional Assistance

Patients without insurance or who do not qualify for copay assistance through AVYXASSIST may qualify for free product assistance. Call an AVYXASSIST Patient Access Specialist to learn more.

Call 866-939-8927 or Fax 833-852-3420 | Monday through Friday, 8:00 AM to 8:00 PM ET

FRINDOVYX Billing and Coding Information

The information provided is for informational purposes only and represents no statement, promise, or guarantee by AVYXA® concerning reimbursement, payment, or charges. The information provided is not intended to increase or maximize reimbursement by any payer. Healthcare professionals are responsible for selecting appropriate codes used to file a claim. Codes should be based on the patient's diagnosis and the items
and services furnished by the healthcare professional. All codes should be verified between the healthcare professional and the payer. AVYXA does not recommend using any particular diagnosis code in billing situations for FRINDOVYX (cyclophosphamide) Injection. The below codes are for reference only; coding as submitted is the sole responsibility of the prescribing physician.

NDCs

Nearly all drugs in the United States are given a unique National Drug Code (NDC), which identifies all currently manufactured drugs and is maintained by the FDA.[2] NDCs are displayed on drug packing in a 10-digit format. Proper NDC billing requires an 11-digit number in a 5-4-2 format, listed below.

FRINDOVYX® NDC	Vial Size
83831-0119-01	Carton of 1 multi-dose vial, 500 mg/mL
83831-0120-02	Carton of 1 multi-dose vial, 1 g/2 mL
83831-0121-04	Carton of 1 multi-dose vial, 2 g/4 mL

HCPCS Code[3]

HCPCS Level II codes are used to identify most drugs and biologics that are given in the office.

FRINDOVYX® Unique J-Code	Description
J9072	Injection, cyclophosphamide (avyxa), 5 mg

J-Code Billing Unit Conversion

Each 5 milligrams of FRINDOVYX® equals one (1) billing unit. When billing for quantities greater than 5 milligrams, indicate the total amount used as a multiple of billing units on the claim form. Examples:

One (1) Vial (1 mL) or 500 mg	100 billing units
One (1) Vial (2 ml) or 1 g	200 billing units
One (1) Vial (4 ml) or 2 g	400 billing units

NOTE: The are a few HCPCS codes for cyclophosphamide, however there is only one code for **FRINDOVYX (J9072)**, so please make sure the HCPCS code matches the product purchased and administered.

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

CPT Drug Administration Codes[4,5]

CPT codes are used to bill drug administration services provided in the physician's office and other outpatient settings.

CPT Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96417	Chemotherapy administration, intravenous infusion technique; each additional sequential infusion (different substance/drug), up to 1 hour

FRINDOVYX® is supplied as a multi-dose vial. Medicare will not pay for drug waste on multi-dose vials, so the JW and JZ modifiers are not applicable in the billing of FRINDOVYX®.[6]

ICD Diagnosis Codes[7,8]

International Classification of Disease, 10th Edition, Clinical Modification Codes for FRINDOVYX®	
Indication	**ICD-10-CM Codes**
Adenocarcinoma of the Ovary	C56.1, C56.2, C56.3, C56.9
Carcinoma of the Breast	C50.011, C50.012, C50.019, C50.021, C50.022, C50.029, C50.111, C50.112, C50.119, C50.121, C50.122, C50.129, C50.211, C50.212, C50.219, C50.221, C50.222, C50.229, C50.311, C50.312, C50.319, C50.321, C50.322, C50.329, C50.411, C50.412, C50.419, C50.421, C50.422, C50.429, C50.511, C50.512, C50.519, C50.521, C50.522, C50.529, C50.611, C50.612, C50.619, C50.621, C50.622, C50.629, C50.811, C50.812, C50.819, C50.821, C50.822, C50.829, C50.911, C50.912, C50.919, C50.921, C50.922, C50.929
Leukemia	C92.1, C92.10, C92.12, C92.0, C92.00, C92.02, C93.0, C93.00, C93.02, C91.0, C91.00, C91.02
Malignant Lymphomas	C81.0, C81.00, C81.01, C81.02, C81.03, C81.04, C81.05, C81.06, C81.07, C81.08, C81.09, C81.1, C81.10, C81.11, C81.12, C81.13, C81.14, C81.15, C81.16, C81.17, C81.18, C81.19, C81.2, C81.20, C81.21, C81.22, C81.23, C81.24, C81.25, C81.26, C81.27, C81.28, C81.29, C81.3, C81.30, C81.31, C81.32, C81.33, C81.34, C81.35, C81.36, C81.37, C81.38, C81.39, C81.4, C81.40, C81.41, C81.42, C81.43, C81.44, C81.45, C81.46, C81.47, C81.48, C81.49, C81.9, C81.90, C81.91, C81.92, C81.93, C81.94, C81.95, C81.96, C81.97, C81.98, C81.99, C83.5, C83.50, C83.51, C83.52, C83.53, C83.54, C83.55, C83.56, C83.57, C83.58, C83.59, C96.A, C83.7, C83.70, C83.71, C83.72, C83.73, C83.74, C83.75, C83.76, C83.77, C83.78, C83.79

Please refer to the individual payer policy for a list of specific coverage criteria. ICD-10-CM diagnosis code must be clearly and explicitly noted in the patient medical record.
*For drugs with multiple indications, it is best practice to code the most specific ICD-10-CM code within the indication, to justify medical necessity.
AMA: American Medical Association; CMS: Centers for Medicare & Medicaid Services; CPT: Current Procedural Terminology; FARS: Federal Acquisition Regulation Supplement; HHSARS: Health and Human Services Acquisition Regulation; ICD: International Classification of Diseases NDC: National Drug Codes

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

ICD Diagnosis Codes[7,8]

International Classification of Disease, 10th Edition, Clinical Modification Codes for FRINDOVYX®	
Indication	**ICD-10-CM Codes**
Multiple Myeloma	C90.00, C90.02
Mycosis Fungoides	C84.00, C84.01, C84.02, C84.03, C84.04, C84.05, C84.06, C84.07, C84.08, C84.09
Neuroblastoma	C74.0, C74.00, C74.01, C74.02, C74.1, C74.10, C74.11, C74.12, C74.9, C74.90, C74.91, C74.92, C72.0, C72.1, C72.2, C72.20, C72.21, C72.22, C72.3, C72.30, C72.31, C72.32, C72.4, C72.40, C72.41, C72.42, C72.5, C72.50, C72.59, C72.9, C49.0, C49.8, C49.9
Retinoblastoma	C69.2, C69.20, C69.21, C69.22

ICD Diagnosis Codes by Indication

ICD-10-CM coding for FRINDOVYX varies greatly by payer. Please check with each payer to ascertain the best coding for FRINDOVYX according to their policy.

Adenocarcinoma of the Ovary: ICD-10-CM Diagnosis Coding	
ICD-10 Code	**Descriptor**
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.3	Malignant neoplasm of bilateral ovaries
C56.9	Malignant neoplasm of unspecified ovary

Carcinoma of the Breast: ICD-10-CM Diagnosis Coding	
ICD-10 Code	**Descriptor**
C50.011 - C50.019	Malignant neoplasm of nipple and areola, female
C50.021 - C50.029	Malignant neoplasm of nipple and areola, male
C50.111 - C50.119	Malignant neoplasm of central portion of breast, female
C50.121 - C50.129	Malignant neoplasm of central portion of breast, male
C50.211 - C50.219	Malignant neoplasm of upper-inner quadrant of breast, female
C50.221 - C50.229	Malignant neoplasm of upper-inner quadrant of breast, male
C50.311 - C50.319	Malignant neoplasm of lower-inner quadrant of breast, female
C50.321 - C50.329	Malignant neoplasm of lower-inner quadrant of breast, male
C50.411 - C50.419	Malignant neoplasm of upper-outer quadrant of breast, female
C50.421 - C50.429	Malignant neoplasm of upper-outer quadrant of breast, male
C50.511 - C50.519	Malignant neoplasm of lower-outer quadrant of breast, female
C50.521 - C50.529	Malignant neoplasm of lower-outer quadrant of breast, male

Carcinoma of the Breast: ICD-10-CM Diagnosis Coding	
ICD-10 Code	**Descriptor**
C50.611 - C50.619	Malignant neoplasm of axillary tail of breast, female
C50.621 - C50.629	Malignant neoplasm of axillary tail of breast, male
C50.811 - C50.819	Malignant neoplasm of overlapping sites of breast, female
C50.821 - C50.829	Malignant neoplasm of overlapping sites of breast, male
C50.911 - C50.919	Malignant neoplasm of breast of unspecified site, female
C50.921 - C50.929	Malignant neoplasm of breast of unspecified site, male

Leukemia: ICD-10-CM Diagnosis Coding	
Chronic Granulocytic Leukemia	
ICD-10 Code	**Descriptor**
C92.1	Chronic myeloid leukemia, BCR/ABL-positive
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.12	Chronic myeloid leukemia, BCR/ABL-positive, in relapse
Acute Myelogenous Leukemia	
ICD-10 Code	**Descriptor**
C92.0	Acute myeloblastic leukemia
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.02	Acute myeloblastic leukemia, in relapse
Monocytic Leukemia	
ICD-10 Code	**Descriptor**
C93.0	Acute monoblastic/monocytic leukemia
C93.00	Acute monoblastic/monocytic leukemia, not having achieved remission
C93.02	Acute monoblastic/monocytic leukemia, in relapse
Acute Lymphoblastic (Stem-Cell) Leukemia	
ICD-10 Code	**Descriptor**
C91.0	Acute lymphoblastic leukemia
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, in relapse

Malignant Lymphoma: ICD-10-CM Diagnosis Coding	
Hodgkin's Disease	
ICD-10 Code	**Descriptor**
C81	Hodgkin lymphoma
C81.0	Nodular lymphocyte predominant Hodgkin lymphoma
C81.00	Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site
C81.01	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.02	Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes
C81.03	Nodular lymphocyte predominant Hodgkin lymphoma, intra-abdominal lymph nodes
C81.04	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.05	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.06	Nodular lymphocyte predominant Hodgkin lymphoma, intrapelvic lymph nodes
C81.07	Nodular lymphocyte predominant Hodgkin lymphoma, spleen
C81.08	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of multiple sites
C81.09	Nodular lymphocyte predominant Hodgkin lymphoma, extranodal and solid organ sites
C81.1	Nodular sclerosis Hodgkin lymphoma
C81.10	Nodular sclerosis Hodgkin lymphoma, unspecified site
C92.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C92.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph node
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.2	Mixed cellularity Hodgkin lymphoma
C81.20	Mixed cellularity Hodgkin lymphoma, unspecified site
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb

Malignant Lymphoma: ICD-10-CM Diagnosis Coding	
Hodgkin's Disease	
ICD-10 Code	**Descriptor**
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.3	Lymphocyte depleted Hodgkin lymphoma
C81.30	Lymphocyte depleted Hodgkin lymphoma, unspecified site
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.4	Lymphocyte-rich Hodgkin lymphoma
C81.40	Lymphocyte-rich Hodgkin lymphoma, unspecified site
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.9	Hodgkin lymphoma, unspecified
C81.90	Hodgkin lymphoma, unspecified, unspecified site
C81.91	Hodgkin lymphoma, unspecified, lymph nodes of head, face, and neck
C81.92	Hodgkin lymphoma, unspecified, intrathoracic lymph nodes

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX® .

Malignant Lymphoma: ICD-10-CM Diagnosis Coding	
Hodgkin's Disease	
ICD-10 Code	**Descriptor**
C81.93	Hodgkin lymphoma, unspecified, intra-abdominal lymph nodes
C81.94	Hodgkin lymphoma, unspecified, lymph nodes of axilla and upper limb
C81.95	Hodgkin lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C81.96	Hodgkin lymphoma, unspecified, intrapelvic lymph nodes
C81.97	Hodgkin lymphoma, unspecified, spleen
C81.98	Hodgkin lymphoma, unspecified, lymph nodes of multiple sites
C81.99	Hodgkin lymphoma, unspecified, extranodal and solid organ sites
Lymphocytic Lymphoma (Diffuse and Nodular)	
ICD-10 Code	**Descriptor**
C83.5	Lymphoblastic (diffuse) lymphoma
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes
C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites
Histiocytic Lymphoma	
ICD-10 Code	**Descriptor**
C96.A	Histiocytic Sarcoma
Burkitt's Lymphoma	
ICD-10 Code	**Descriptor**
C83.7	Burkitt Lymphoma
C83.70	Burkitt lymphoma, unspecified site
C83.71	Burkitt lymphoma, lymph nodes of head, face, and neck
C83.72	Burkitt lymphoma, intrathoracic lymph nodes
C83.73	Burkitt lymphoma, intra-abdominal lymph nodes

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

Malignant Lymphoma: ICD-10-CM Diagnosis Coding	
Burkitt's Lymphoma	
ICD-10	**Descriptor**
C83.74	Burkitt lymphoma, lymph nodes of axilla and upper limb
C83.75	Burkitt lymphoma, lymph nodes of inguinal region and lower limb
C83.76	Burkitt lymphoma, intrapelvic lymph nodes
C83.77	Burkitt lymphoma, spleen
C83.78	Burkitt lymphoma, lymph nodes of multiple sites
C83.79	Burkitt lymphoma, extranodal and solid organ sites

Multiple Myeloma: ICD-10-CM Diagnosis Coding	
ICD-10	**Descriptor**
C90.0	Multiple myeloma
C90.00	Multiple myeloma, not having achieved remission
C90.02	Multiple myeloma, in relapse

Mycosis Fungoides: ICD-10-CM Diagnosis Coding	
ICD-10	**Descriptor**
C84.0	Mycosis fungoides
C84.00	Mycosis fungoides, unspecified site
C84.01	Mycosis fungoides, lymph nodes of head, face, and neck
C84.02	Mycosis fungoides, intrathoracic lymph nodes
C84.03	Mycosis fungoides, intra-abdominal lymph nodes
C84.04	Mycosis fungoides, lymph nodes of axilla and upper limb
C84.05	Mycosis fungoides, lymph nodes of inguinal region and lower limb
C84.06	Mycosis fungoides, intrapelvic lymph nodes
C84.07	Mycosis fungoides, spleen
C84.08	Mycosis fungoides, lymph nodes of multiple sites
C84.09	Mycosis fungoides, extranodal and solid organ sites

Neuroblastoma: ICD-10-CM Diagnosis Coding	
ICD-10	**Descriptor**
C74.0	Malignant neoplasm of cortex of adrenal gland
C74.00	Malignant neoplasm of cortex of unspecified adrenal gland

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

Neuroblastoma: ICD-10-CM Diagnosis Coding	
ICD-10	**Descriptor**
C74.01	Malignant neoplasm of cortex of right adrenal gland
C74.02	Malignant neoplasm of cortex of left adrenal gland
C74.1	Malignant neoplasm of medulla of adrenal gland
C74.10	Malignant neoplasm of medulla of unspecified adrenal gland
C74.11	Malignant neoplasm of medulla of right adrenal gland
C74.12	Malignant neoplasm of medulla of left adrenal gland
C74.9	Malignant neoplasm of unspecified part of adrenal gland
C74.90	Malignant neoplasm of unspecified part of unspecified adrenal gland
C74.91	Malignant neoplasm of unspecified part of right adrenal gland
C74.92	Malignant neoplasm of unspecified part of left adrenal gland
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C72.2	Malignant neoplasm of olfactory nerve
C72.20	Malignant neoplasm of unspecified olfactory nerve
C72.21	Malignant neoplasm of right olfactory nerve
C72.22	Malignant neoplasm of left olfactory nerve
C72.3	Malignant neoplasm of optic nerve
C72.30	Malignant neoplasm of unspecified optic nerve
C72.31	Malignant neoplasm of right optic nerve
C72.32	Malignant neoplasm of left optic nerve
C72.4	Malignant neoplasm of acoustic nerve
C72.40	Malignant neoplasm of unspecified acoustic nerve
C72.41	Malignant neoplasm of right acoustic nerve
C72.42	Malignant neoplasm of left acoustic nerve
C72.5	Malignant neoplasm of other and unspecified cranial nerves
C72.50	Malignant neoplasm of unspecified cranial nerve
C72.59	Malignant neoplasm of other cranial nerves
C72.9	Malignant neoplasm of central nervous system, unspecified
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified

Retinoblastoma: ICD-10-CM Diagnosis Coding	
ICD-10 Code	**Descriptor**
C69.2	Malignant neoplasm of retina
C69.20	Malignant neoplasm of unspecified retina
C69.21	Malignant neoplasm of right retina
C69.22	Malignant neoplasm of left retina

Sample UB-04 / CMS 1450 Claim Form

Form Locator (FL) 42

(Electronic Claim Form = Loop 2400, Segment Type SV201):

List the appropriate revenue code for the drug. Match the descriptor for FRINDOVYX® Injection to your revenue code, 0636.

Additionally, enter an appropriate revenue code for the administration service, 0335 for chemotherapy, or others based on the cost center in which the service was performed.

FL 43

(NOT REQUIRED BY MEDICARE):

Enter the description of the procedure for the Revenue Code billed.

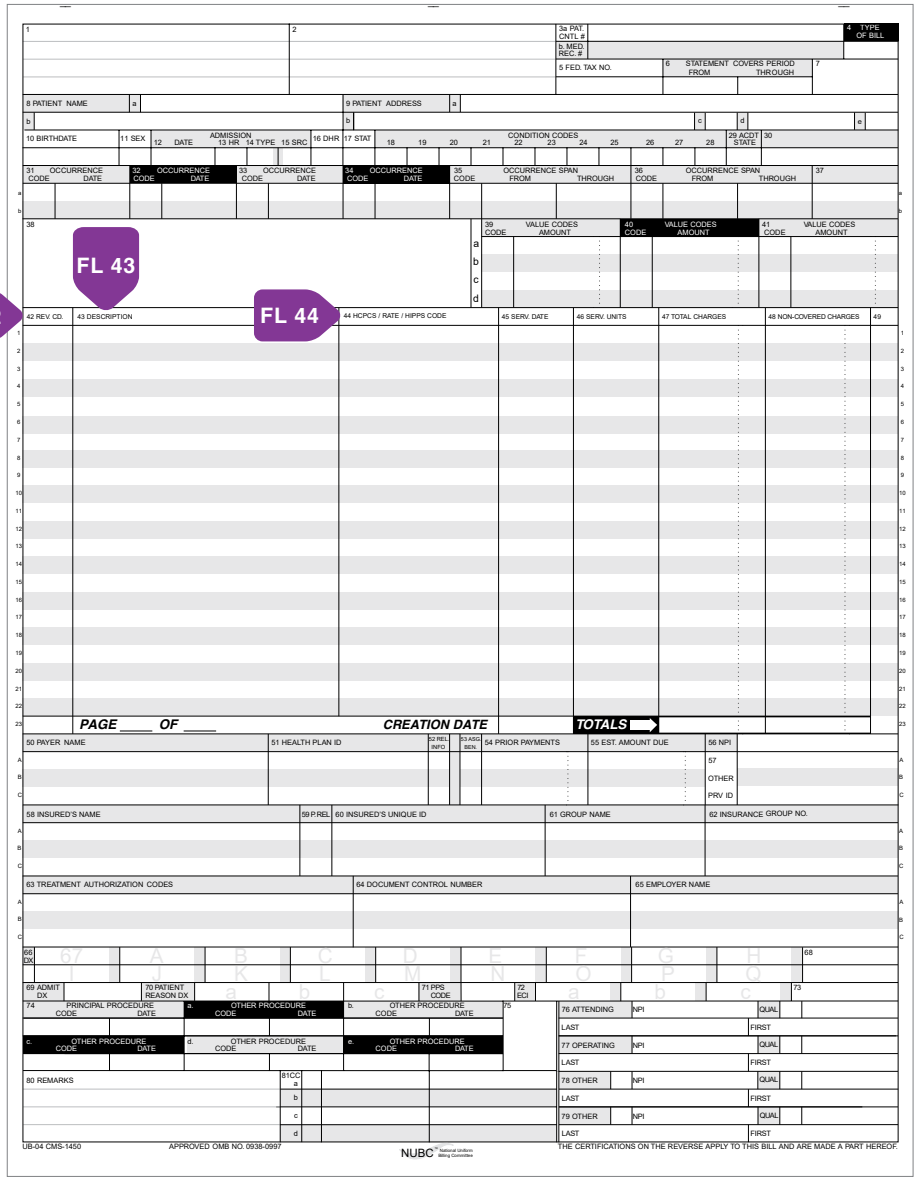
If required, list the N4 indicator first, then the 11-digit NDC code. In the third place, list the NDC unit measurement code and, last, the quantity. Check with other payers for their requirements.

FL 44

(Electronic Claim Form = Loop 2400, SV202-1 = HC/HP):

Enter the appropriate HCPCS code - **J9072, Injection, cyclophosphamide (AVYXA), 5 mg.**

For administration, enter the appropriate code or codes for the infusion duration. As an example, a 60-minute infusion of chemotherapy requires 96413.[1]



Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

FL 45

(Electronic Claim Form = Loop 2400, Segment DTP/472/03):

Enter the date of service

FL 46

FL 46 (Electronic Claim Form = Loop 2400, SV205):

Enter the units for the HCPCS code billed. Enter the number of service units for each item.

For example, 100 units if using one 500 mg/mL multi-dose vial of FRINDOVYX® Injection.

FL 63

(Electronic Claim Form = Loop 2300, REF/G1/02):

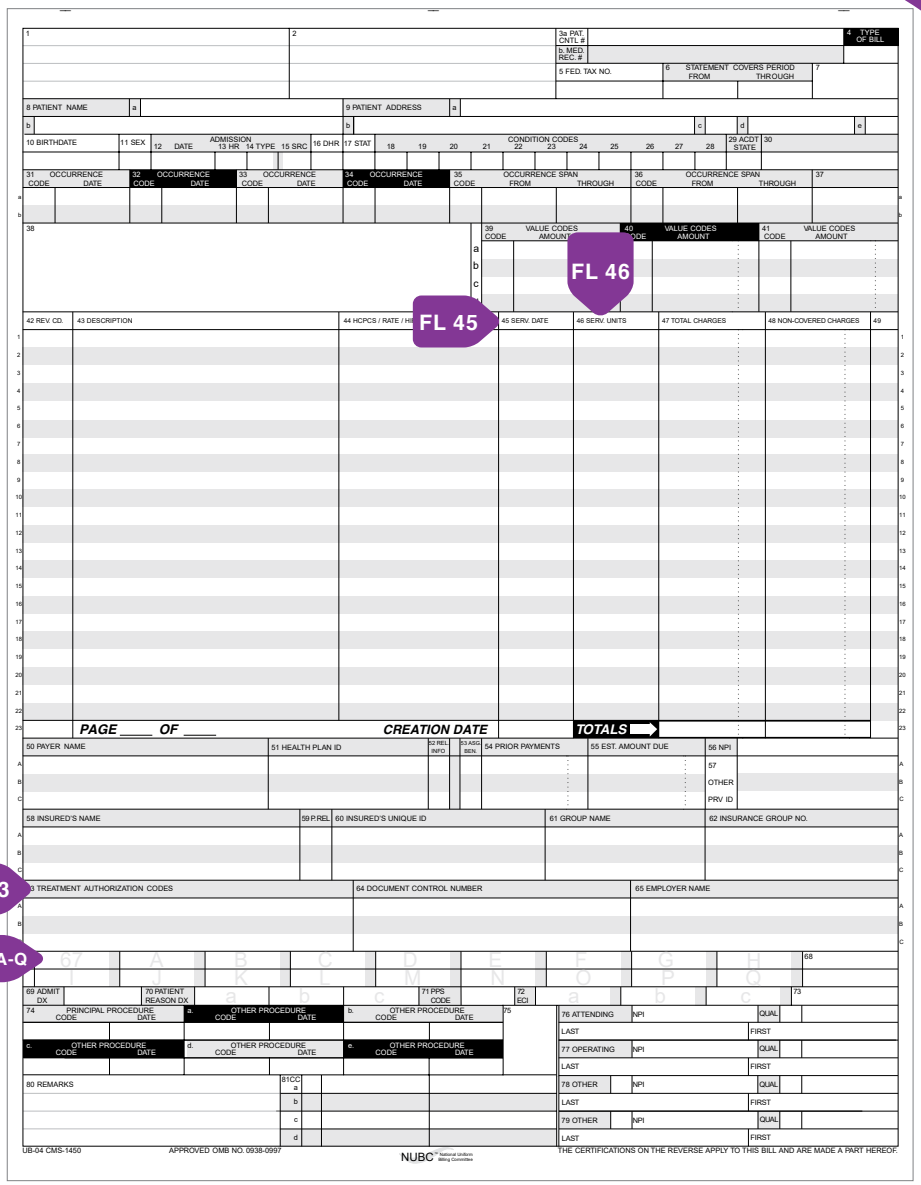
Enter treatment authorization code.

FL 67A-Q

(Electronic Claim Form Loop 2300, H101-2 (H101-1=BK):

Enter a diagnosis code for the drug documented in the medical record. Be as specific as possible.

The code listed here is an example: **C50.111, Malignant neoplasm of central portion of right female breast.**



[1] CPT Code 96413 Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug. Initial infusion times may vary.

Electronic Claims Reference: *ASC 837I Version 5010A2 Institutional Health Care Claim to theCMS-1450 Claim Form Crosswalk." Palmettogba.Com. Palmetto GBA, Accessed April 3, 2023. https://www.palmettogba.com/pal-%20metto/providers.nsf/files/EDI_837I_v5010A2_crosswalk.pdf/$FILE/EDI_837I_v5010A2_crosswalk.pdf*

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

Sample CMS 1500 Claim Form

Box 21

(Electronic Claim Form = Loop 2300, Segment H101-2 through H112=2):

Enter the patient's diagnosis from the patient's medical record.

An example code for this drug is **C50.111, Malignant neoplasm of central portion of right female breast**

Use Box 21 B-L fields for secondary diagnoses.

Box 23

(Electronic Claim Form = Loop 2300, REF02):

Enter prior authorization number if one exists.

Box 24D

(Electronic Claim Form = Loop 2400, Segment SV101):

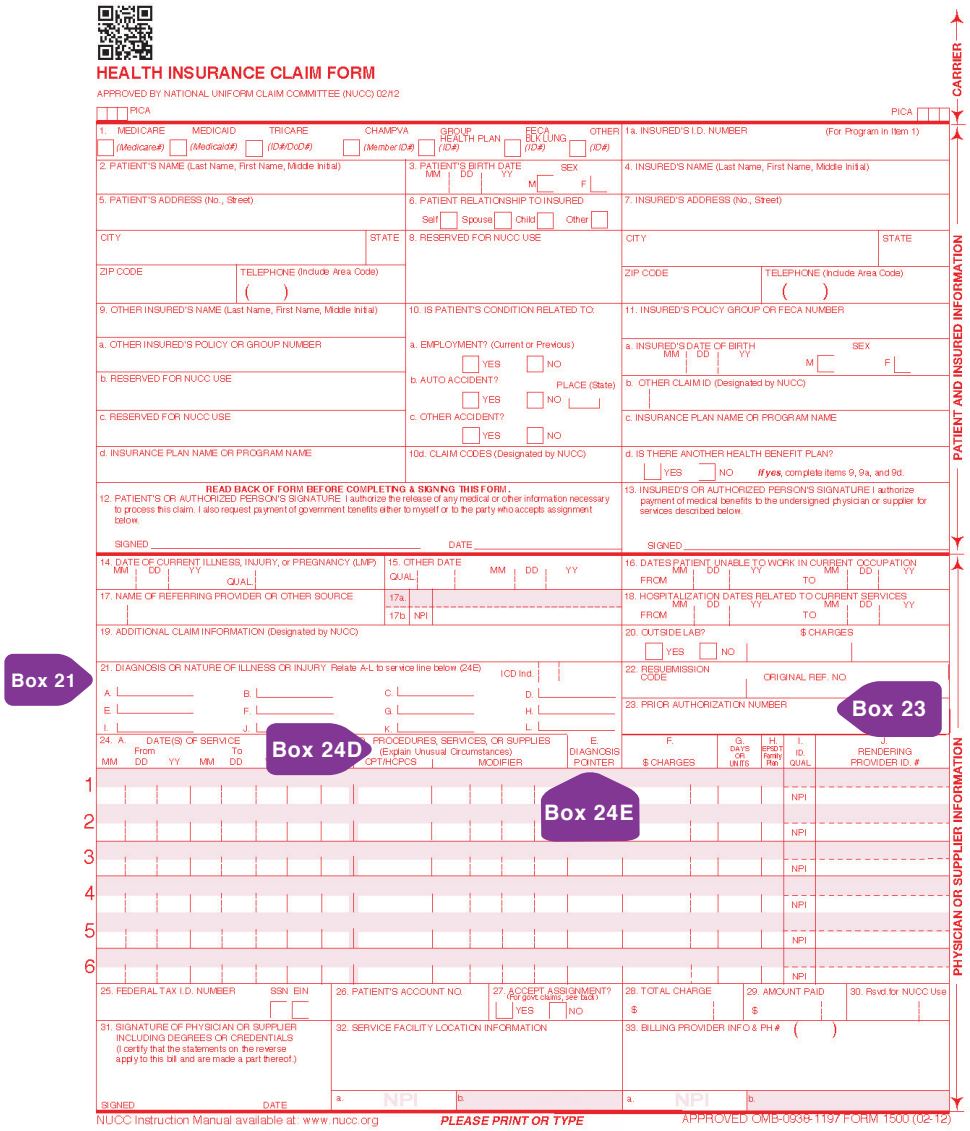
Enter the appropriate HCPCS code - **J9072, Injection, cyclophosphamide, (avyxa), 5mg**

For administration, enter the appropriate code or codes for the infusion duration. As an example, **a 60-minute infusion of chemotherapy requires 96413.[1]**

Box 24E

(Electronic Claim Form = Loop 2400, Segment SV107):

Specify the diagnosis letter that corresponds with the drug and drug administration code(s) in Box 21.



Box 24G

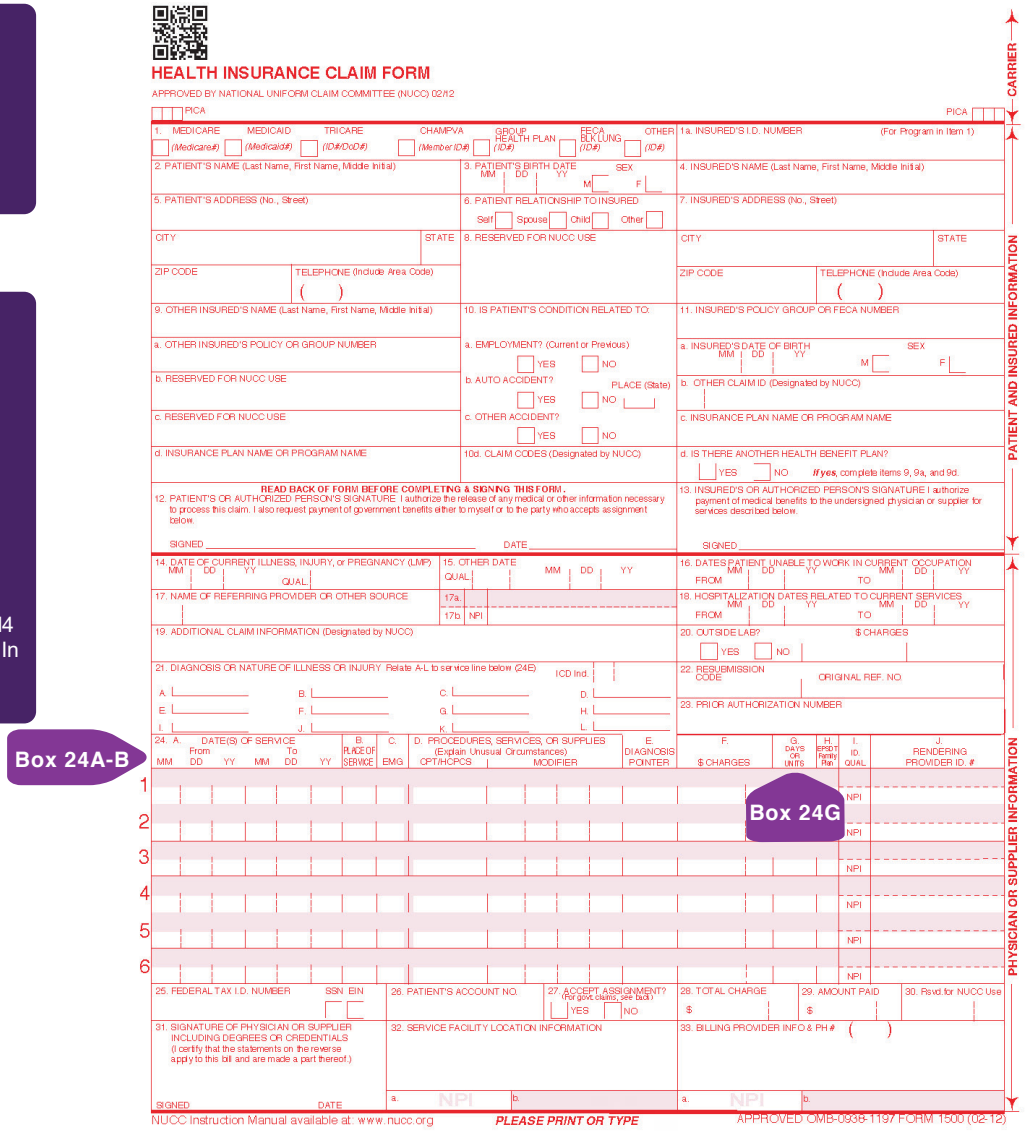
(Electronic Claim Form = Loop 2400, SV104):

Enter the number of service units for each item.

Box 24A-B

(Electronic Claim Form: Box 24A (Electronic Claims = Loop 2400, DTP02; Box 24 B (Loop 2300/2400, Segment CLM05-1/SV105)

In the non-shaded area, enter the appropriate date of service and place of service code.
Example: Physician Office = 11.
If required, in the shaded area, enter the N4 indicator first, then the 11-digit NDC code. In the third space, list the NDC unit measurement code, and last, the quantity.



[1] CPT Code 96413 Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug. Initial infusion times may vary.

Electronic Claims Reference: *ASC 837I Version 5010A2 Institutional Health Care Claim to theCMS-1450 Claim Form Crosswalk." Palmettogba.Com. Palmetto GBA, Accessed April 3, 2023. https://www.palmettogba.com/pal-%20metto/providers.nsf/files/EDI_837I_v5010A2_crosswalk.pdf/$FILE/EDI_837I_v5010A2_crosswalk.pdf*

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections

Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia and anemia), bone marrow failure, and severe immunosuppression which may lead to serious and sometimes fatal infections, including sepsis and septic shock. Latent infections can be reactivated.

Antimicrobial prophylaxis may be indicated in certain cases of neutropenia at the discretion of the managing physician. In case of neutropenic fever, antibiotic therapy is indicated. Antimycotics and/or antivirals may also be indicated.

Monitoring of complete blood counts is essential during cyclophosphamide treatment so that the dose can be adjusted, if needed. Cyclophosphamide should not be administered to patients with neutrophils ≤1,500/mm^3 and platelets <50,000/mm^3. Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection. G-CSF may be administered to reduce the risks of neutropenia complications associated with cyclophosphamide use. Primary and secondary prophylaxis with G-CSF should be considered in all patients considered to be at increased risk for neutropenia complications. The nadirs of the reduction in leukocyte count and thrombocyte count are usually reached in weeks 1 and 2 of treatment. Peripheral blood cell counts are expected to normalize after approximately 20 days. Bone marrow failure has been reported. Severe myelosuppression may be expected particularly in patients pretreated with and/or receiving concomitant chemotherapy and/or radiation therapy.

Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide. Medical and/or surgical supportive treatment may be required to treat protracted cases of severe hemorrhagic cystitis. Discontinue cyclophosphamide therapy in case of severe hemorrhagic cystitis.

Urotoxicity (bladder ulceration, necrosis, fibrosis, contracture and secondary cancer) may require interruption of cyclophosphamide treatment or cystectomy. Urotoxicity can be fatal. Urotoxicity can occur with short-term or long-term use of cyclophosphamide.

Before starting treatment, exclude or correct any urinary tract obstructions. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of urotoxicity and/or nephrotoxicity. Cyclophosphamide should be used with caution, if at all, in patients with active urinary tract infections. Aggressive hydration with forced diuresis and frequent bladder emptying can reduce the frequency and severity of bladder toxicity. Mesna has been used to prevent severe bladder toxicity.

Cardiotoxicity

Myocarditis, myopericarditis, pericardial effusion including cardiac tamponade, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide therapy.

Supraventricular arrhythmias (including atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported after treatment with regimens that included cyclophosphamide.

The risk of cardiotoxicity may be increased with high doses of cyclophosphamide, in patients with advanced age, and in patients with previous radiation treatment to the cardiac region and/or previous or concomitant treatment with other cardiotoxic agents.

Particular caution is necessary in patients with risk factors for cardiotoxicity and in patients with preexisting cardiac disease.

Monitor patients with risk factors for cardiotoxicity and with pre-existing cardiac disease.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Pulmonary Toxicity

Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide. Late onset pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with increased mortality. Pneumonitis may develop years after treatment with cyclophosphamide.

Monitor patients for signs and symptoms of pulmonary toxicity.

Secondary Malignancies

Cyclophosphamide is genotoxic. Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens. The risk of bladder cancer may be reduced by prevention of hemorrhagic cystitis.

Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOD) including fatal outcome has been reported in patients receiving cyclophosphamide- containing regimens. A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other agents has been identified as a major risk factor. VOD has also been reported to develop gradually in patients receiving long-term low-dose immunosuppressive doses of cyclophosphamide.Other risk factors predisposing to the development of VOD include preexisting disturbances of hepatic function, previous radiation therapy of the abdomen, and a low performance status.

Alcohol Content

The alcohol content in a dose of FRINDOVYX® may affect the central nervous system and should be taken into account for patients in whom alcohol intake should be avoided or minimized. Consideration should be given to the alcohol content in FRINDOVYX on the ability to drive or use machines immediately after the infusion. Each administration of FRINDOVYX at 50 mg per kg delivers 0.0448 g/kg of ethanol. For a 75 kg patient this would deliver 3.36 grams of ethanol. Other cyclophosphamide products may have a different amount of alcohol or no alcohol.

Embryo-Fetal Toxicity

Based on its mechanism of action and published reports of effects in pregnant patients or animals, FRINDOVYX can cause fetal harm when administered to a pregnant woman. Exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects in the newborn. Cyclophosphamide is teratogenic and embryo-fetal toxic in mice, rats, rabbits and monkeys.

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with FRINDOVYX and for up to 1 year after completion of therapy. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with FRINDOVYX and for 4 months after completion of therapy.

Please see Important Safety Information on pages 3 and 19-27 and full Prescribing Information for FRINDOVYX®.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Infertility

Male and female reproductive function and fertility may be impaired in patients being treated with FRINDOVYX®. Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide, duration of therapy, and the state of gonadal function at the time of treatment. Cyclophosphamide-induced sterility may be irreversible in some patients. Advise patients on the potential risks for infertility.

Impairment of Wound Healing

Cyclophosphamide may interfere with normal wound healing.

Hyponatremia

Hyponatremia associated with increased total body water, acute water intoxication, and a syndrome resembling SIADH (syndrome of inappropriate secretion of antidiuretic hormone), which may be fatal, has been reported.

ADVERSE REACTIONS

Please see “Warnings and Precautions, Contraindications, and Use in Specific Populations” for more information on the following adverse reactions:

- Hypersensitivity
- Myelosuppression, Immunosuppression, Bone Marrow Failure, and Infections
- Urinary Tract and Renal Toxicity
- Cardiotoxicity
- Pulmonary Toxicity
- Secondary Malignancies
- Veno-occlusive Liver Disease
- Alcohol Content
- Infertility
- Impaired Wound Healing
- Hyponatremia

Clinical Trials and Postmarketing Experience

The following adverse reactions associated with the use of cyclophosphamide were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most common adverse reactions were neutropenia, febrile neutropenia, fever, alopecia, nausea, vomiting, and diarrhea.

Cardiac: cardiac arrest, ventricular fibrillation, ventricular tachycardia, cardiogenic shock, pericardial effusion (progressing to cardiac tamponade), myocardial hemorrhage, myocardial infarction, cardiac failure (including fatal outcomes), cardiomyopathy, myocarditis, pericarditis, carditis, atrial fibrillation, supraventricular arrhythmia, ventricular arrhythmia, bradycardia, tachycardia, palpitations, QT prolongation.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Congenital, Familial and Genetic: intra-uterine death, fetal malformation, fetal growth retardation, fetal toxicity (including myelosuppression, gastroenteritis).

Ear and Labyrinth: deafness, hearing impaired, tinnitus.

Endocrine: water intoxication.

Eye: visual impairment, conjunctivitis, lacrimation.

Gastrointestinal: gastrointestinal hemorrhage, acute pancreatitis, colitis, enteritis, cecitis, stomatitis, constipation, parotid gland inflammation, nausea, vomiting, diarrhea.

General Disorders and Administrative Site Conditions: multiorgan failure, general physical deterioration, influenza-like illness, injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema), pyrexia, edema, chest pain, mucosal inflammation, asthenia, pain, chills, fatigue, malaise, headache, febrile neutropenia.

Hematologic: myelosuppression, bone marrow failure, disseminated intravascular coagulation and hemolytic uremic syndrome (with thrombotic microangiopathy).

Hepatic: veno-occlusive liver disease, cholestatic hepatitis, cytolytic hepatitis, hepatitis, cholestasis; hepatotoxicity with hepatic failure, hepatic encephalopathy, ascites, hepatomegaly, blood bilirubin increased, hepatic function abnormal, hepatic enzymes increased.

Immune: immunosuppression, anaphylactic shock and hypersensitivity reaction.

Infections: The following manifestations have been associated with myelosuppression and immunosuppression caused by cyclophosphamide: increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal and, parasitic infections; reactivation of latent infections, (including viral hepatitis, tuberculosis), *Pneumocystis jiroveci*, herpes zoster, *Strongyloides*, sepsis and septic shock.

Investigations: blood lactate dehydrogenase increased, C-reactive protein increased.

Metabolism and Nutrition: hyponatremia, fluid retention, blood glucose increased, blood glucose decreased.

Musculoskeletal and Connective Tissue: rhabdomyolysis, scleroderma, muscle spasms, myalgia, arthralgia.

Neoplasms: acute leukemia, myelodysplastic syndrome, lymphoma, sarcomas, renal cell carcinoma, renal pelvis cancer, bladder cancer, ureteric cancer, thyroid cancer.

Nervous System: encephalopathy, convulsion, dizziness, neurotoxicity has been reported and manifested as reversible posterior leukoencephalopathy syndrome, myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia, parosmia.

Pregnancy: premature labor.

Psychiatric: confusional state.

Renal and Urinary: renal failure, renal tubular disorder, renal impairment, nephropathy toxic, hemorrhagic cystitis, bladder necrosis, cystitis ulcerative, bladder contracture, hematuria, nephrogenic diabetes insipidus, atypical urinary bladder epithelial cells.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Reproductive System: infertility, ovarian failure, ovarian disorder, amenorrhea, oligomenorrhea, testicular atrophy, azoospermia, oligospermia.

Respiratory: pulmonary veno-occlusive disease, acute respiratory distress syndrome, interstitial lung disease as manifested by respiratory failure (including fatal outcomes), obliterative bronchiolitis, organizing pneumonia, alveolitis allergic, pneumonitis, pulmonary hemorrhage; respiratory distress, pulmonary hypertension, pulmonary edema, pleural effusion, bronchospasm, dyspnea, hypoxia, cough, nasal congestion, nasal discomfort, oropharyngeal pain, rhinorrhea.

Skin and Subcutaneous Tissue: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, radiation recall dermatitis, toxic skin eruption, urticaria, dermatitis, blister, pruritus, erythema, nail disorder, facial swelling, hyperhidrosis, alopecia.

Tumor lysis syndrome: like other cytotoxic drugs, cyclophosphamide may induce tumor-lysis syndrome and hyperuricemia in patients with rapidly growing tumors.

Vascular: pulmonary embolism, venous thrombosis, vasculitis, peripheral ischemia, hypertension, hypotension, flushing, hot flush.

DRUG INTERACTIONS

Effect of Other Drugs on Cyclophosphamide Exposure

Protease Inhibitors

Concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites and may enhance the toxicities of cyclophosphamide, including higher incidence of infections, neutropenia, and mucositis. Monitor for increased toxicities in patients receiving protease inhibitors.

Drugs that Potentiate Cyclophosphamide Toxicities

Drugs or agents with similar toxicities to FRINDOVYX® and can potentiate these effects are listed below.

Drugs that increase hematotoxicity and/or immunosuppression

- ACE inhibitors: ACE inhibitors can cause leukopenia
- Natalizumab
- Paclitaxel: Increased hematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion
- Thiazide diuretics
- Zidovudine

Drugs that increase cardiotoxicity

- Anthracyclines
- Cytarabine
- Pentostatin
- Radiation therapy of the cardiac region
- Trastuzumab

IMPORTANT SAFETY INFORMATION (CONTINUED)

Drugs that increase pulmonary toxicity

- Amiodarone
- G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor)

Drugs that increase nephrotoxicity

- Amphotericin B
- Indomethacin: Acute water intoxication has been reported with concomitant use of indomethacin

Drugs that potentiate increase in other toxicities

- Azathioprine: Increased risk of hepatotoxicity (liver necrosis)
- Busulfan: Increased incidence of hepatic veno-occlusive disease and mucositis has been reported
- Protease inhibitors: Increased incidence of mucositis

Drugs that increase the risk of hemorrhagic cystitis

- Radiation treatment: Increased risk of hemorrhagic cystitis may result from a combined effect of cyclophosphamide and past or concomitant radiation treatment

Effect of Cyclophosphamide on Other Drugs

Metronidazole

Acute encephalopathy has been reported in a patient receiving cyclophosphamide and metronidazole. Monitor for neurologic toxicities in patients receiving metronidazole.

Tamoxifen

Concomitant use of tamoxifen and a cyclophosphamide-containing chemotherapy regimen may increase the risk of thromboembolic complications. Monitor for signs and symptoms of thromboembolic events in patients receiving tamoxifen.

Coumarins

Both increased and decreased warfarin effect have been reported in patients receiving warfarin and cyclophosphamide. Monitor anticoagulant activity closely in patients receiving warfarin or other coumarins.

Cyclosporine

Concomitant administration of cyclophosphamide may decrease serum concentrations of cyclosporine. This interaction may result in an increased incidence of graft-versus-host disease. Monitor for signs and symptoms of graft-versus-host disease in patients receiving cyclosporine.

Depolarizing Muscle Relaxants

If a patient has been treated with cyclophosphamide within 10 days of general anesthesia, alert the anesthesiologist.

Cyclophosphamide treatment causes a marked and persistent inhibition of cholinesterase activity. Prolonged apnea may occur with concurrent depolarizing muscle relaxants (e.g., succinylcholine).

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on its mechanism of action and published reports of effects in pregnant patients or animals, FRINDOVYX® can cause fetal harm when administered to a pregnant woman. Exposure to cyclophosphamide during pregnancy may cause fetal malformations, miscarriage, fetal growth retardation, and toxic effects in the newborn *[see Data below].* Cyclophosphamide is teratogenic and embryo-fetal toxic in mice, rats, rabbits and monkeys *[see Data below].* Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Human Data

Malformations of the skeleton, palate, limbs and eyes as well as miscarriage have been reported after exposure to cyclophosphamide in the first trimester. Fetal growth retardation and toxic effects manifesting in the newborn, including leukopenia, anemia, pancytopenia, severe bone marrow hypoplasia, and gastroenteritis have been reported after exposure to cyclophosphamide.

Animal Data

Administration of cyclophosphamide to pregnant mice, rats, rabbits and monkeys during the period of organogenesis at doses at or below the dose in patients based on body surface area resulted in various malformations, which included neural tube defects, limb and digit defects and other skeletal anomalies, cleft lip and palate, and reduced skeletal ossification.

Lactation

Risk Summary

Cyclophosphamide is present in breast milk. Neutropenia, thrombocytopenia, low hemoglobin, and diarrhea have been reported in infants breast fed by women treated with cyclophosphamide. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with FRINDOVYX and for 1 week after the last dose.

Females and Males of Reproductive Potential

FRINDOVYX can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of FRINDOVYX®.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with FRINDOVYX® and for up to 1 year after completion of therapy.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with FRINDOVYX and for 4 months after completion of therapy.

Infertility

Females

Amenorrhea, transient or permanent, associated with decreased estrogen and increased gonadotropin secretion develops in a proportion of women treated with cyclophosphamide. Affected patients generally resume regular menses within a few months after cessation of therapy. The risk of premature menopause with cyclophosphamide increases with age. Oligomenorrhea has also been reported in association with cyclophosphamide treatment.

Animal data suggest an increased risk of failed pregnancy and malformations may persist after discontinuation of cyclophosphamide as long as oocytes/follicles exist that were exposed to cyclophosphamide during any of their maturation phases. The exact duration of follicular development in humans is not known, but may be longer than 12 months.

Males

Men treated with cyclophosphamide may develop oligospermia or azoospermia which are normally associated with increased gonadotropin but normal testosterone secretion.

Pediatric Use

The safety and effectiveness of FRINDOVYX have been established in pediatric patients and information on this use is discussed throughout the full Patient information.

The alcohol content of FRINDOVYX should be taken into account when given to pediatric patients.

Pre-pubescent females who receive cyclophosphamide generally develop secondary sexual characteristics normally and have regular menses. Ovarian fibrosis with apparently complete loss of germ cells after prolonged administration of cyclophosphamide in late pre-pubescence has been reported. Females who received cyclophosphamide who have retained ovarian function after completing treatment are at increased risk of developing premature menopause.

Pre-pubescent males who receive cyclophosphamide develop secondary sexual characteristics normally, but may have oligospermia or azoospermia and increased gonadotropin secretion. Some degree of testicular atrophy may occur. Cyclophosphamide-induced azoospermia is reversible in some patients, though the reversibility may not occur for several years after cessation of therapy.

IMPORTANT SAFETY INFORMATION (CONTINUED)

Geriatric Use

There is insufficient data from clinical studies of cyclophosphamide available for patients 65 years of age and older to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac functioning, and of concomitant disease or other drug therapy.

Renal Impairment

In patients with severe renal impairment, decreased renal excretion may result in increased plasma levels of cyclophosphamide and its metabolites which may increase toxicity. Monitor patients with severe renal impairment (CL_{Cr}=10 mL/min to 24 mL/min) for signs and symptoms of toxicity.

Cyclophosphamide and its metabolites are dialyzable although there are probably quantitative differences depending upon the dialysis system. In patients requiring dialysis, consider using a consistent interval between cyclophosphamide administration and dialysis.

Hepatic Impairment

Patients with severe hepatic impairment have reduced conversion of cyclophosphamide to the active 4-hydroxyl metabolite, potentially reducing efficacy. Monitor patients with severe hepatic impairment (total bilirubin > 3 x ULN and any aspartate aminotransferase (AST)) for reduced effectiveness of cyclophosphamide.

The alcohol content of FRINDOVYX® should be taken into account when given to patients with hepatic impairment.

OVERDOSAGE

No specific antidote for cyclophosphamide is known.

Overdosage should be managed with supportive measures, including appropriate treatment for any concurrent infection, myelosuppression, or cardiac toxicity should it occur.

Serious consequences of overdosage include manifestations of dose dependent toxicities such as myelosuppression, urotoxicity, cardiotoxicity (including cardiac failure), veno-occlusive hepatic disease, and stomatitis.

Patients who received an overdose should be closely monitored for the development of toxicities, and hematologic toxicity in particular.

Cyclophosphamide and its metabolites are dialyzable. Therefore, rapid hemodialysis is indicated when treating any suicidal or accidental overdose or intoxication.

Cystitis prophylaxis with mesna may be helpful in preventing or limiting urotoxic effects with cyclophosphamide overdose.

Please see the full Prescribing Information for safety information, and dosing guidelines.

To report SUSPECTED ADVERSE REACTIONS, contact Avyxa Pharma, LLC at 1-888-520-0954 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Notes

References:

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7. CDC. Classification of Diseases, Functioning, and Disability. Accessed January 27, 2025. https://www.cdc.gov/nchs/icd/
8. CDC. National Center for Health Statistics. ICD-10-CM Fiscal Year Releases. January 27, 2025. https://www.cdc.gov/nchs/icd/icd-10-cm/files.html

AVYXA