

Fludarabine

Phosphate Injection, USP

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary		
Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
intra-venous	Sterile Injectible Liquid, 25 mg/mL	For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

INDICATIONS AND CLINICAL USE

Fludarabine Phosphate Injection, USP is indicated for:

- second-line treatment in patients with chronic lymphocytic leukemia (CLL) and low-grade non-Hodgkin's lymphoma (Lg-NHL) who have failed other conventional therapies.

Geriatrics (> 75 years of age)

Since there are limited data for the use of fludarabine phosphate in elderly persons (> 75 years), caution should be exercised with the administration of fludarabine phosphate in these patients. The total body clearance of the principal plasma metabolite 2F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Patients with reduced kidney function demonstrated an increased total body exposure (area under the curve [AUC] of 2F-ara-A). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 mL/min). Since renal impairment is frequently present in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 mL/min, the dose should be reduced by up to 50% and close hematologic monitoring should be used to assess toxicity. Fludarabine phosphate treatments are contraindicated if creatinine clearance is < 30 mL/min. (See **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**.)

Pediatrics

The safety and effectiveness of fludarabine phosphate in children have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Renally impaired patients with creatinine clearance < 30 mL/min.
- Patients with decompensated hemolytic anemia.
- In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory CLL, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate in combination with pentostatin is contraindicated.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Fludarabine phosphate should be administered under the supervision of, or prescribed by, a qualified physician experienced in the use of antineoplastic therapy.

Fludarabine phosphate is associated with:

- Myelosuppression (see **WARNINGS AND PRECAUTIONS, Hematologic**)
- Irreversible CNS effects (see **WARNINGS AND PRECAUTIONS, Neurologic**)
- Auto-immune hemolytic anemia (see **WARNINGS AND PRECAUTIONS, Hematologic**)

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory CLL, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate in combination with pentostatin is contraindicated.

General

Fludarabine phosphate is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of hematologic and nonhematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of neutropenia, thrombocytopenia, anemia and leukopenia.

Vaccination with live vaccines should be avoided during and after treatment with fludarabine phosphate.

Carcinogenesis and Mutagenesis

Disease progression and transformation (e.g., Richter's Syndrome) have been commonly reported in CLL patients (see **WARNINGS AND PRECAUTIONS, Skin**).

Endocrine and Metabolism

Tumor lysis syndrome associated with fludarabine phosphate treatment has been reported in CLL patients with large tumor burdens. Since fludarabine phosphate can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

Gastrointestinal

In clinical trials with oral fludarabine phosphate, nausea/vomiting and/or diarrhea were reported in approximately 38% of patients. In most cases, the severity was mild to moderate (WHO toxicity grading). Only a small percentage of patients, approximately 1% with nausea/vomiting and 5% with diarrhea, required therapy. Patients with prolonged, clinically relevant, nausea/vomiting and diarrhea should be closely monitored to avoid dehydration.

Hematologic

In patients with an impaired state of health, fludarabine phosphate should be given with caution and after careful risk/benefit consideration. This applies especially to patients with severe impairment of bone marrow function (thrombocytopenia, anemia and/or granulocytopenia), immunodeficiency or with a history of opportunistic infection. Prophylactic treatment should be considered in patients at increased risk of developing opportunistic infections (see **ADVERSE REACTIONS**).

Bone marrow suppression, notably thrombocytopenia, anemia, leukopenia and neutropenia, may occur with administration of fludarabine phosphate and requires careful hematologic monitoring. In a Phase I study in solid tumor patients, the median time to nadir counts was 13 days (range, 3 - 25 days) for granulocytes and 16 days (range, 2 - 32 days) for platelets. Most patients had hematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate requires careful hematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The

duration of clinically significant cytopenia in the cases reported has ranged from approximately 2 months to approximately 1 year. These episodes have occurred in both previously treated and untreated patients.

Instances of life-threatening and sometimes fatal autoimmune phenomena (e.g., autoimmune hemolytic anemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, acquired hemophilia and Evans' syndrome) have been reported to occur during or after treatment with fludarabine phosphate in patients with or without a previous history of autoimmune processes or a positive Coombs' test and who may or may not be in remission from their disease. Steroids may or may not be effective in controlling these hemolytic episodes. One study was performed with 31 patients with hemolytic anemia related to the administration of fludarabine phosphate. Since the majority (90%) of these patients rechallenged with fludarabine phosphate developed a recurrence in the hemolytic process, rechallenge with fludarabine phosphate should be avoided. The mechanisms which predispose patients to the development of this complication have not been identified. Patients undergoing treatment with fludarabine phosphate should be evaluated and closely monitored for signs of autoimmune hemolytic anemia (a decline in hemoglobin linked with hemolysis and a positive Coombs' test). Discontinuation of therapy with fludarabine phosphate is recommended in the event of hemolysis. The transfusion of irradiated blood and the administration of corticosteroids are the most common treatment measures for autoimmune hemolytic anemia.

Hepatic/Biliary/Pancreatic

No data are available concerning the use of fludarabine phosphate in patients with hepatic impairment. In this group of patients, fludarabine phosphate should be used with caution and administered if the perceived benefit outweighs any potential risk.

Immune

Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been observed after transfusion of nonirradiated blood in patients treated with fludarabine phosphate. Fatal outcome as a consequence of this disease has been reported with a high frequency. Therefore, to minimize the risk of transfusion-associated graft-versus-host disease, patients who require blood transfusion and who are undergoing or who have received treatment with fludarabine phosphate should receive irradiated blood only.

Neurologic

When high doses of fludarabine phosphate were administered in dose-ranging studies in acute leukemia patients, a syndrome with delayed onset, characterized by blindness, coma and death was identified. Symptoms appeared from 21 to 60 days post dosing (however, in postmarketing experience, cases of neurotoxicity have been reported to occur both earlier and later than seen in clinical trials). Demyelination, especially of the occipital cortex of the brain was noted. The majority of these cases occurred in patients treated intravenously with doses approximately four times greater (96 mg/m²/day for 5 - 7 days) than the recommended dose. Thirteen of 36 patients (36.1%) who received fludarabine phosphate at high doses (≥ 96 mg/m²/day for 5 to 7 days per course) developed severe neurotoxicity, while only one of 443 patients (0.2%) who received the drug at low doses (≤ 40 mg/m²/day for 5 days per course) developed the toxicity. In patients treated at doses in the range of the dose recommended for CLL and Lg-NHL, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion).

The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown. In some studies, however, patients tolerated the recommended dose for relatively long treatment periods (up to 26 courses of therapy). Periodic neurological assessments are recommended.

Renal

The total body clearance of the principal plasma metabolite 2F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal

excretion pathway for the elimination of the compound. Patients with reduced renal function demonstrated an increased total body exposure (AUC of 2F-ara-A). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 mL/min). Therefore, if renal impairment is clinically suspected, or in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 mL/min, the dose should be reduced by up to 50% and close hematological monitoring should be used to assess toxicity. Fludarabine phosphate treatments are contraindicated if creatinine clearance is < 30 mL/min. (See **DOSAGE AND ADMINISTRATION**.)

Sexual Function/Reproduction

Preclinical toxicology studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. The possible adverse effects on fertility in males and females in humans have not been adequately evaluated. Therefore, it is recommended that men and women of child-bearing potential take contraceptive measures during fludarabine phosphate therapy and for at least 6 months after the cessation of fludarabine phosphate therapy.

Skin

The worsening or flare-up of pre-existing skin cancer lesions as well as new onset of skin cancer have been reported to occur in patients during or after intravenous fludarabine phosphate therapy.

Special Populations

Pregnant Women: There are very limited data of fludarabine phosphate use in pregnant women in the first trimester: one newborn has been described with absent bilateral radii and normal thumbs, thrombocytopenia, fossa ovalis aneurysm and a small patent ductus arteriosus. Early pregnancy loss has been reported in fludarabine phosphate monotherapy as well as in combination therapy. Premature delivery has been reported.

Fludarabine phosphate should not be used during pregnancy unless clearly necessary (e.g., life-threatening situation, no alternative safer treatment available without compromising the therapeutic benefit, treatment cannot be avoided). It has the potential to cause fetal harm. Prescribers may only consider it to be used if the potential benefits justify the potential risks to the fetus. Women of childbearing potential must be apprised of the potential hazard to the fetus.

Women should avoid becoming pregnant while on fludarabine phosphate therapy. Women of childbearing potential or fertile males must take effective contraceptive measures during and at least for 6 months after cessation of therapy.

Nursing Women: Breast-feeding should not be initiated during fludarabine phosphate treatment. Nursing women should discontinue breast-feeding. There is evidence from preclinical data after intravenous administration to rats that fludarabine phosphate and/or metabolites transfer from maternal blood to milk.

Pediatrics: The safety and effectiveness of fludarabine phosphate in children have not been established.

Geriatrics (> 75 years of age): Since there are limited data for the use of fludarabine phosphate in elderly persons (> 75 years), caution should be exercised with the administration of fludarabine phosphate in these patients. The total body clearance of the principal plasma metabolite 2F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Patients with reduced kidney function demonstrated an increased total body exposure (AUC of 2F-ara-A). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 mL/min). Since renal impairment is frequently present in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 mL/min, the dose should be reduced by up to 50% and close hematologic monitoring should be used to assess toxicity. Fludarabine phosphate treatments are

contraindicated if creatinine clearance is < 30 mL/min. (See **DOSAGE AND ADMINISTRATION**.)

Monitoring and Laboratory Tests

During treatment, the patient's hematologic (particularly neutrophils and platelets) and serum chemistry profiles should be monitored regularly.

Effects on Ability to Drive and Operate Machines

Fludarabine phosphate may reduce the ability to drive or use machines, since fatigue, weakness, and visual disturbances have been observed.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events occurring with fludarabine phosphate use include myelosuppression (anemia, leukopenia, neutropenia and thrombocytopenia), leading to decreased resistance to infection, including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting and diarrhea. Other commonly reported events include chills, edema, malaise, peripheral neuropathy, visual disturbance, anorexia, mucositis, stomatitis and skin rash. Serious opportunistic infections have occurred in patients treated with fludarabine phosphate. Fatalities as a consequence of serious adverse events have been reported.

Table 2 below reports adverse events by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data regardless of the causal relationship with fludarabine phosphate. The rare adverse reactions were mainly identified from post-marketing experience.

DRUG INTERACTIONS

Serious Drug Interactions

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory CLL, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of Fludarabine Phosphate Injection, USP in combination with pentostatin is contraindicated.

Drug-Drug Interactions

The therapeutic efficacy of fludarabine phosphate may be reduced by dipyrindamole and other inhibitors of adenosine uptake.

Clinical studies and *in vitro* experiments showed that using fludarabine phosphate in combination with cytarabine may increase the intracellular concentration and intracellular exposure of Ara-CTP (active metabolite of cytarabine) in leukemic cells. Plasma concentrations of Ara-C and the elimination rate of Ara-C were not affected.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Incompatibilities:

The formulation for intravenous use must not be mixed with other drugs.

Recommended Dose and Dosage Adjustment

The usual starting dose of Fludarabine Phosphate Injection, USP is 25 mg/m² administered intravenously over a period of approximately 30 minutes, daily for five days every 28 days. Dosage may be decreased based on evidence of hematologic or nonhematologic toxicity.

Note that in patients with decreased renal function (creatinine clearance between 30 and 70 mL/min), the dose should be reduced by up to 50%. Fludarabine Phosphate Injection treatment is contraindicated if creatinine clearance is < 30 mL/min. (See **WARNINGS AND PRECAUTIONS**.)

The duration of treatment depends on the treatment success and the tolerability of the drug. Fludarabine

Phosphate Injection should be administered until the achievement of a maximal response (complete or partial remission, usually 6 cycles) and then the drug should be discontinued.

Administration

Studies in animals have shown that even in cases of misplaced injections, no relevant local irritation was observed after paravenous, intraarterial and intramuscular administration of an aqueous solution containing 7.5 mg fludarabine phosphate/mL.

It is strongly recommended that Fludarabine Phosphate Injection should only be administered intravenously. No cases have been reported in which paravenously administered fludarabine phosphate led to severe local adverse reactions. However, unintentional paravenous administration should be avoided.

The product may be diluted for intravenous administration to a concentration of 1 mg/mL in 5% Dextrose Injection USP or in 0.9% Sodium Chloride Injection USP.

OVERDOSAGE

Higher than recommended doses of fludarabine phosphate have been associated with an irreversible central nervous system toxicity characterized by delayed blindness, coma and death. High doses are also associated with bone marrow suppression manifested by thrombocytopenia and neutropenia. There is no known specific antidote for fludarabine phosphate overdose. Treatment consists of drug discontinuation and supportive therapy.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fludarabine phosphate is a fluorinated analog of adenine that is relatively resistant to deamination by adenosine deaminase.

Fludarabine phosphate (2F-ara-AMP) is a water-soluble prodrug, which is rapidly dephosphorylated to 2-fluoro-ara-A (2F-ara-A) and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate 2-fluoro-ara-ATP (2F-ara-ATP). The antitumor activity of this metabolite is the result of inhibition of DNA synthesis via inhibition of ribonucleotide reductase, DNA polymerase α , δ and ϵ , DNA primase, and DNA ligase. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur. While some aspects of the mechanism of action of 2F-ara-ATP are as yet unclear, it is believed that effects on DNA, RNA and protein synthesis all contribute to the inhibition of cell growth, with inhibition of DNA synthesis being the dominant factor. In addition, *in vitro* studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and apoptosis.

Two open-label studies of fludarabine phosphate have been conducted in patients with CLL refractory to at least one prior standard alkylating agent-containing regimen. Overall objective response rates were 32% in one study, and 48% in the other with median time to response at 21 and 7 weeks respectively.

Pharmacokinetics

Cellular pharmacokinetics of fludarabine triphosphate: Maximum 2F-ara-ATP levels in leukemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited considerable variation with a median peak concentration of approximately 20 μ M. 2F-ara-ATP levels in leukemic cells were always considerably higher than maximum 2F-ara-A levels in the plasma, indicating an accumulation at the target sites. *In vitro* incubation of leukemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F-ara-A enrichment. Two independent investigations respectively reported median half-life values of 15 and 23 hours for the elimination of 2F-ara-ATP from target cells.

No clear correlation was found between 2F-ara-A pharmacokinetics and treatment efficacy in cancer patients; however, the occurrence of neutropenia and hematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses hematopoiesis in a dose-dependent manner.

Plasma and urinary pharmacokinetics of fludarabine (2F-ara-A):

Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2F-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2F-ara-A pharmacokinetics. After single doses of 25 mg 2F-ara-AMP/m² to cancer patients infused over 30 minutes, 2F-ara-A reached mean maximum concentrations in the plasma of 3.5 - 3.7 µM at the end of infusion. Corresponding 2F-ara-A levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4 - 4.8 µM at the end of infusion. During a 5-day treatment cycle, 2F-ara-A plasma trough levels increased by a factor of about 2. Accumulation of 2F-ara-A over several treatment cycles does not occur. Post maximum levels decayed in three disposition phases with an initial half-life of approximately 5 minutes, an intermediate half-life of 1 - 2 hours and a terminal half-life of approximately 20 hours.

An interstudy comparison of 2F-ara-A pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 mL/min/m² (2.2 mL/min/kg) and a mean volume of distribution (V_d) of 83 L/m² (2.4 L/kg). The data showed a high interindividual variability. After i.v. and peroral administration of fludarabine phosphate, plasma levels of 2F-ara-A and areas under the plasma level time curves increased linearly with the dose, whereas half-lives, plasma clearance and volumes of distribution remained constant independent of the dose, indicating a dose-linear behaviour.

The mean steady-state volume of distribution (V_{dss}) of 2F-ara-A in one study was 96 L/m², suggesting a significant degree of tissue binding. Another study, in which V_{dss} for patients was determined to be 44 L/m², supports the suggestion of tissue binding.

Based upon compartmental analysis of pharmacokinetic data, the rate-limiting step for excretion of 2F-ara-A from the body appears to be release from tissue binding sites. Total body clearance of 2F-ara-A has been shown to be inversely correlated with serum creatinine, suggesting renal elimination of the compound.

Special Populations and Conditions

Renal Insufficiency: A pharmacokinetic study in patients with and without renal impairment revealed that, in patients with normal renal function, 40 to 60% of the administered i.v. dose was excreted in the urine. Mass balance studies in laboratory animals with ³H-2F-ara-AMP showed a complete recovery of radio-labelled substances in the urine. Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was observed in humans only to a minor extent. Patients with impaired renal function exhibited a reduced total body clearance, indicating the need for a reduced dose. Total body clearance of 2F-ara-A has been shown to be inversely correlated with serum creatinine, suggesting renal elimination of the compound. This was confirmed in a study of the pharmacokinetics of 2F-ara-A following administration of 2F-ara-AMP to cancer patients with normal renal function or varying degrees of renal impairment.

The total body clearance of the principal metabolite 2F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Renal clearance represented on average 40% of the total body clearance. *In vitro* investigations with human plasma proteins revealed no pronounced tendency of 2F-ara-A protein binding.

STORAGE AND STABILITY

Store Fludarabine Phosphate Injection, USP under refrigeration between 2 and 8°C (36 and 46°F). Fludarabine Phosphate Injection contains no antimicrobial preservative and thus care must be taken to ensure the sterility of prepared solutions. Discard unused portion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

SPECIAL HANDLING INSTRUCTIONS

Fludarabine Phosphate Injection, USP should not be handled by pregnant staff. Proper handling and disposal procedures should be observed, with consideration given to the guidelines used for cytotoxic drugs. Any spillage or waste material may be disposed of by incineration.

Caution should be exercised in the preparation of the Fludarabine Phosphate Injection. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution comes into contact with the skin or mucous membranes, the area should be washed thoroughly with soap and water. In the event of contact with the eyes, rinse them thoroughly with copious amounts of water. Exposure by inhalation should be avoided.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Fludarabine Phosphate Injection, USP

Medicinal ingredients: Each mL of sterile injectable liquid contains 25 mg of fludarabine phosphate.

Non-medicinal ingredients: Each mL of sterile injectable liquid contains 25 mg of mannitol; water for injection, qs; and sodium hydroxide to adjust the pH to 6.8.

pH: 6.0 - 7.1

Availability: Fludarabine Phosphate Injection, USP for intravenous injection is supplied as a 2-mL single-dose vial packaged in an individual carton.

Vial stoppers do not contain natural rubber latex.

PHARMACEUTICAL PARTNERS OF CANADA INC.
Richmond Hill, ON L4B 3P6

☎ 1 877 821-7724

Table 2: Fludarabine Phosphate Clinical Trial Adverse Events (by MedDRA SOC)				
System Organ Class MedDRA	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Infections and infestations	Infections / opportunistic infections (like latent viral reactivation, e.g., herpes zoster virus, Epstein-Barr virus, progressive multifocal leucoencephalopathy), pneumonia			Lymphoproliferative disorder (EBV-associated)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		Myelodysplastic syndrome and acute myeloid leukemia (mainly associated with prior, concomitant, or subsequent treatment with alkylating agents, topoisomerase inhibitors or irradiation)		
Blood and lymphatic system disorders	Neutropenia, anemia, thrombocytopenia	Myelosuppression		
Immune system disorders			Autoimmune disorder (including autoimmune hemolytic anemia, thrombocytopenic purpura, pemphigus, Evans' syndrome, acquired hemophilia)	
Metabolism and nutrition disorders		Anorexia	Tumor lysis syndrome (including renal failure, hyperkalemia, metabolic acidosis, hematuria, urate crystalluria, hyperuricemia, hyperphosphatemia, hypocalcemia)	
Nervous system disorders		Neuropathy peripheral	Confusion	Agitation, seizures, coma
Eye disorders		Visual disturbance		Optic neuritis, optic neuropathy, blindness
Cardiac disorders				Heart failure, arrhythmia
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (including dyspnea, pulmonary fibrosis, pneumonitis)	
Gastrointestinal disorders	Nausea, vomiting, diarrhea	Stomatitis	Gastrointestinal hemorrhage, pancreatic enzymes abnormal	
Hepatobiliary disorders			Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Rash		Skin cancer, Stevens-Johnson syndrome, necrolysis epidermal toxic (Lyell type)
Renal and urinary disorder				Hemorrhagic cystitis
General disorders and administration site conditions	Fever, fatigue, weakness	Chills, malaise, edema, mucositis		