Ifosfamide: Drug information

(For additional information see "Ifosfamide: Patient drug information" and see "Ifosfamide: Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Bone marrow suppression:

Myelosuppression can be severe and lead to fatal infections. Monitor blood counts prior to and at intervals after each treatment cycle.

CNS toxicity:

CNS toxicities can be severe and result in encephalopathy and death. Monitor for CNS toxicity and discontinue treatment for encephalopathy.

Hemorrhagic cystitis:

Hemorrhagic cystitis can be severe and can be reduced by the prophylactic use of mesna.

Nephrotoxicity:

Nephrotoxicity can be severe and result in renal failure.

Brand Names: US

Ifex

Brand Names: Canada

Ifex; Ifosfamide for Injection

Pharmacologic Category

Antineoplastic Agent, Alkylating Agent; Antineoplastic Agent, Alkylating Agent (Nitrogen Mustard)

Dosing: Adult

Note: To prevent bladder toxicity, ifosfamide should be given with mesna and hydration (at least 2 L of oral or IV fluid per day). Ifosfamide is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Roila 2010).

Testicular cancer: IV:

Manufacturer's labeling; as part of combination chemotherapy and with mesna: 1,200 mg/m^2/day for 5 days every 3 weeks or after hematologic recovery

VIP regimen: 1,200 mg/m^2/day for 5 days every 3 weeks for 4 cycles (in combination with etoposide, mesna, and cisplatin) (Nichols 1998)

VeIP regimen: 1,200 mg/m^2/day for 5 days every 3 weeks for 4 cycles (in combination with vinblastine, mesna, and cisplatin) (Loehrer 1998)

Off-label dosing/combinations:

TIP regimen (off-label dosing): 1,500 mg/m^2/day for 4 days (days 2 to 5) every 3 weeks for 4 cycles (in combination with paclitaxel, mesna, and cisplatin) (Kondagunta 2005)

TICE regimen (off-label dosing): 2,000 mg/m^2/day for 3 days (days 2 to 4) over 4 hours every 2 weeks for 2 cycles (in combination with paclitaxel and mesna; followed by carboplatin and etoposide) (Kondagunta 2007)

Bladder cancer, advanced (off-label use): IV: 1,500 mg/m^2/day for 5 days every 3 weeks (with mesna) until disease progression (Witte 1997)

Cervical cancer, recurrent or metastatic (off-label use): IV: 1,500 mg/m^2/day for 5 days every 3 weeks (with mesna) (Coleman 1986; Sutton 1993)

Ewing sarcoma (off-label use): IV:

VAC/IE regimen: Adults ≤30 years: IE: 1,800 mg/m^2/day for 5 days (in combination with mesna and etoposide) alternate with VAC (vincristine, doxorubicin, and cyclophosphamide) every 3 weeks for a total of 17 courses (Grier 2003)

VAIA regimen: 3,000 mg/m^2 day on days 1, 2, 22, 23, 43, and 44 for 4 courses (in combination with vincristine, doxorubicin, dactinomycin, and mesna) (Paulussen 2001) **or** Adults ≤35 years: 2,000 mg/m^2/day for 3 days every 3 weeks for 14 courses (in combination with vincristine, doxorubicin, dactinomycin, and mesna) (Paulussen 2008)

VIDE regimen: Adults ≤50 years: 3,000 mg/m^2/day over 1 to 3 hours for 3 days every 3 weeks for 6 courses (in combination with vincristine, doxorubicin, etoposide, and mesna) (Juergens 2006)

IE regimen: 1,800 mg/m^2/day over 1 hour for 5 days every 3 weeks for 12 cycles (in combination with etoposide and mesna) (Miser 1987)

ICE regimen: Adults ≤22 years: 1,800 mg/m^2/day for 5 days every 3 weeks for up to 12 cycles (in combination with carboplatin and etoposide [and mesna]) (van Winkle 2005)

Hodgkin lymphoma, relapsed or refractory (off-label use): IV:

ICE regimen: 5,000 mg/m^2 (over 24 hours) beginning on day 2 every 2 weeks for 2 cycles (in combination with mesna, carboplatin, and etoposide) (Moskowitz 2001)

IGEV regimen: 2,000 mg/m^2/day for 4 days every 3 weeks for 4 cycles (in combination with mesna, gemcitabine, vinorelbine, and prednisolone) (Santoro 2007)

Non-Hodgkin lymphomas (off-label use): IV:

Burkitt lymphoma (CODOX-M/IVAC regimen):

Adults ≤65 years: Cycles 2 and 4 (IVAC): 1,500 mg/m^2/day for 5 days (IVAC is combination with cytarabine, mesna, and etoposide; IVAC alternates with CODOX-M) (Mead 2008)

Adults >65 years: Cycles 2 and 4 (IVAC): 1,000 mg/m^2/day for 5 days (IVAC is combination with cytarabine, mesna, and etoposide; IVAC alternates with CODOX-M) (Mead 2008)

Diffuse large B-cell lymphoma (RICE regimen): 5,000 mg/m^2 (over 24 hours) beginning on day 4 every 2 weeks for 3 cycles (in combination with mesna, carboplatin, etoposide, and rituximab) (Kewalramani 2004)

Osteosarcoma (off-label use): IV:

Ifosfamide/cisplatin/doxorubicin/HDMT regimen: Adults <40 years: 3,000 mg/m^2/day continuous infusion for 5 days during weeks 4 and 10 (preop) and during weeks 16, 25, and 34 (postop) (in combination with cisplatin, doxorubicin, methotrexate [high-dose], and mesna) (Bacci 2003)

Ifosfamide/cisplatin/epirubicin regimen: 2,000 mg/m^2/day over 4 hours for 3 days (days 2, 3, and 4) every 3 weeks for 3 cycles (preop) and every 4 weeks for 3 cycles (postop) (in combination with cisplatin, epirubicin, and mesna) (Basaran 2007)

ICE regimen (adults ≤22 years): 1,800 mg/m^2/day for 5 days every 3 weeks for up to 12 cycles (in combination with carboplatin and etoposide [and mesna]) (van Winkle 2005)

Ovarian cancer, advanced (platinum-resistant): IV: 1,000 to 1,200 mg/m^2/day for 5 days (with mesna) every 28 days for up to 6 cycles (Markman 1992). Additional trials may be necessary to further define the role of ifosfamide in this condition.

Soft tissue sarcoma (off-label use): IV:

Single-agent ifosfamide: 3,000 mg/m^2/day over 4 hours for 3 days every 3 weeks for at least 2 cycles or until disease progression (van Oosterom 2002)

EIA regimen: 1,500 mg/m^2/day for 4 days every 3 weeks until disease progression or unacceptable toxicity (in combination with etoposide, doxorubicin, and regional hyperthermia) (Issels 2010)

MAID regimen: 2,000 mg/m^2/day continuous infusion for 3 days every 3 weeks (in combination with mesna, doxorubicin, and dacarbazine) (Antman 1993; Antman 1998) **or** 2,500 mg/m^2/day continuous infusion for 3 days every 3 weeks (in combination with mesna, doxorubicin, and dacarbazine); reduce ifosfamide to 1,500 mg/m^2/day if prior pelvic irradiation (Elias 1989)

Ifosfamide/epirubicin: 1,800 mg/m^2/day over 1 hour for 5 days every 3 weeks for 5 cycles (in combination with mesna and epirubicin) (Frustaci 2001)

AIM regimens: 1,500 mg/m^2/day over 2 hours for 4 days every 3 weeks for 4 to 6 cycles (in combination with mesna and doxorubicin) (Worden 2005) **or** 2,000 to 3,000 mg/m^2/day over 3 hours for 3 days (in combination with mesna and doxorubicin) (Grobmyer 2004)

Thymomas and thymic cancers, advanced (off-label use): IV: 1,200 mg/m^2/day for 4 days every 3 weeks for 4 cycles (in combination with mesna, cisplatin, and etoposide); colony-stimulating growth factor support was administered on days 5 to 15 (or until WBC ≥10,000/mm^3) (Loehrer 2001) **or** 1,500 mg/m^2/day for 5 days (with mesna) every 3 weeks for up to 9 cycles (Highley 1999). Additional trials may be necessary to further define the role of ifosfamide in this condition.

Dosing: Pediatric

(For additional information see "Ifosfamide: Pediatric drug information")

Note: To prevent bladder toxicity, ifosfamide should be given with mesna and hydration (at least 2 L of oral or IV fluid per day). Ifosfamide is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Dupuis 2011).

Ewing sarcoma (off-label use): IV:

VAC/IE regimen: IE: 1,800 mg/m^2/day for 5 days (in combination with mesna and etoposide) alternate with VAC (vincristine, doxorubicin, and cyclophosphamide) every 3 weeks for a total of 17 courses (Grier 2003)

ICE-CAV regimen: ICE: 1,800 mg/m^2/day for 5 days every 3 to 4 weeks for 2 courses (in combination with carboplatin and etoposide [and mesna]), followed by CAV (cyclophosphamide, doxorubicin, and vincristine) (Milano 2006)

VAIA regimen: 3,000 mg/m^2/day on days 1, 2, 22, 23, 43, and 44 for 4 courses (in combination with vincristine, doxorubicin, dactinomycin, and mesna) (Paulussen 2001) **or** 2,000 mg/m^2/day for 3 days every 3 weeks for 14 courses (in combination with vincristine, doxorubicin, dactinomycin, and mesna) (Paulussen 2008)

VIDE regimen: 3,000 mg/m^2/day over 1 to 3 hours for 3 days every 3 weeks for 6 courses (in combination with vincristine, doxorubicin, etoposide, and mesna) (Juergens 2006)

IE regimen: 1,800 mg/m^2/day over 1 hour for 5 days every 3 weeks for 12 cycles (in combination with etoposide and mesna) (Miser 1987)

ICE regimen: 1,800 mg/m^2/day for 5 days every 3 weeks for up to 12 cycles (in combination with carboplatin and etoposide [and mesna]) (van Winkle 2005)

Osteosarcoma (off-label use): IV:

Ifosfamide/cisplatin/doxorubicin/HDMT regimen: 3,000 mg/m^2/day continuous infusion for 5 days during weeks 4 and 10 (preop) and during weeks 16, 25, and 34 (postop) (in combination with cisplatin, doxorubicin, methotrexate [high-dose], and mesna) (Bacci 2003)

Ifosfamide/cisplatin/epirubicin regimen: Children ≥15 years: 2,000 mg/m^2/day over 4 hours for 3 days (days 2, 3, and 4) every 3 weeks for 3 cycles (preop) and every 4 weeks for 3 cycles (postop) (in combination with cisplatin, epirubicin, and mesna) (Basaran 2007)

IE regimen: 3,000 mg/m^2/day over 3 hours for 4 days every 3 to 4 weeks (in combination with etoposide and mesna) (Gentet 1997)

ICE regimen: Children ≥1 year: 1,800 mg/m^2/day for 5 days every 3 weeks for up to 12 cycles (in combination with carboplatin and etoposide [and mesna]) (van Winkle 2005)

Ifosfamide/HDMT/etoposide regimen: 3,000 mg/m^2/day over 3 hours for 4 days during weeks 4 and 9 (3 additional postop courses were administered in good responders) (in combination with methotrexate [high-dose], etoposide, and mesna) (Le Deley 2007)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

Consider dosage reduction in patients with renal impairment; however, there are no dosage adjustments provided in the manufacturer's labeling; ifosfamide (and metabolites) are excreted renally and may accumulate in patients with renal dysfunction. Ifosfamide and metabolites are dialyzable.

The following adjustments have also been recommended:

Aronoff 2007:

CrCl ≥10 mL/minute: Children and Adults: No dosage adjustment necessary.

CrCl <10 mL/minute: Children and Adults: Administer 75% of dose.

Hemodialysis (supplement for dialysis):

Children: 1 g/m^2 followed by hemodialysis 6 to 8 hours later

Adults: No supplemental dose needed

Kintzel 1995:

CrCl 46 to 60 mL/minute: Administer 80% of dose

CrCl 31 to 45 mL/minute: Administer 75% of dose

CrCl <30 mL/minute: Administer 70% of dose

Dosing: Hepatic Impairment There are no dosage adjustments provided in the manufacturer's labeling; however, ifosfamide is extensively hepatically metabolized to both active and inactive metabolites; use with caution. The following adjustments have been recommended:

Floyd 2006: Bilirubin >3 mg/dL: Administer 25% of dose.

Dosing: Obesity *ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer:* Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

Dosing: Adjustment for Toxicity

WBC <2,000/mm^3 and/or platelets <50,000/mm^3: Avoid administering treatment (unless clinically necessary)

Encephalopathy: Discontinue treatment

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous:

Generic: 1 g/20 mL (20 mL); 3 g/60 mL (60 mL)

Solution, Intravenous [preservative free]:

Generic: 1 g/20 mL (20 mL); 3 g/60 mL (60 mL)

Solution Reconstituted, Intravenous:

Ifex: 1 g (1 ea); 3 g (1 ea)

Generic: 1 g (1 ea); 3 g (1 ea)

Generic Equivalent Available (US) Yes

Administration Ifosfamide is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2010).

Administer IV over at least 30 minutes (infusion times may vary by protocol; refer to specific protocol for infusion duration). To prevent bladder toxicity, ifosfamide should be given with mesna and hydration.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use **Testicular cancer:** Treatment (third-line) of germ cell testicular cancer (in combination with other chemotherapy drugs and with concurrent mesna for prophylaxis of hemorrhagic cystitis)

Use: Off-Label

Bladder cancer, advanced; Cervical cancer (recurrent or metastatic); Ewing sarcoma; Hodgkin lymphoma, relapsed or refractory; Non-Hodgkin lymphomas; Osteosarcoma; Ovarian cancer, advanced (platinum-resistant); Soft tissue sarcoma; Thymomas and thymic cancers, advanced

Medication Safety Issues

Sound-alike/look-alike issues:

Ifosfamide may be confused with cyclophosphamide

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its

list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

>10%:

Central nervous system: Brain disease (≤15%), central nervous system toxicity (≤15%)

Dermatologic: Alopecia (83% to 90%; combination therapy: 100%)

Endocrine & metabolic: Metabolic acidosis (31%)

Gastrointestinal: Nausea (≤58%), vomiting (≤58%)

Hematologic & oncologic: Leukopenia (≤100%; grade 4: ≤50%; nadir: 8 to 14 days), anemia (38%), thrombocytopenia (20%; grades 3/4: ≤8%)

Renal: Hematuria (6% to 92%, reduced with mesna; grade 2 [gross hematuria]: 8% to 12%)

1% to 10%:

Cardiovascular: Localized phlebitis (2% to 3%)

Gastrointestinal: Anorexia (1%)

Hematologic & oncologic: Febrile neutropenia (1%)

Hepatic: Hepatic insufficiency (2% to 3%), increased serum bilirubin (2% to 3%), increased serum transaminases (2% to 3%)

Infection: Infection (8% to 10%)

Renal: Renal insufficiency (6%)

Miscellaneous: Fever (1%)

<1%, postmarketing, and/or case reports: Abdominal pain, abnormal gait, acute renal failure, agranulocytosis, altered hormone level (increased gonadotropin), amenorrhea, amnesia, anaphylaxis, angina pectoris, angioedema, anovulation, anuria, arthralgia, asterixis, atrial premature contractions, atrial fibrillation, atrial flutter, atrial premature contractions, azoospermia, blood coagulation disorder, blurred vision, bone marrow failure, bradycardia, bradyphrenia, bronchospasm, bundle branch block, capillary leak syndrome, cardiac arrhythmia, cardiac failure, cardiogenic shock, cardiomyopathy, cardiotoxicity, casts in urine, catatonia, chest pain, chills, cholestasis, chronic renal failure, colitis, conjunctivitis, constipation, cough, increased serum creatinine, decreased creatinine clearance, decreased plasma estrogen concentration, deep vein thrombosis, delirium, delusions, dermatitis, diarrhea, disseminated intravascular coagulation, dysarthria, dysesthesia, dyspnea, dysuria, ECG abnormality (QRS complex abnormal), edema, enterocolitis, erythema, extrapyramidal reaction, facial swelling, Fanconi’s syndrome, fatigue, fecal incontinence, flushing, fulminant hepatitis, gastrointestinal hemorrhage, glycosuria, granulocytopenia, growth suppression (children), hearing loss, hemolytic anemia, hemolytic-uremic syndrome, hemorrhage (including myocardial), hemorrhagic cystitis, hepatic failure, hepatic veno-occlusive disease, hepatitis (cytolytic), hepatorenal syndrome, herpes zoster, hyperglycemia, hyperhidrosis, hypertension, hyperpigmentation, hypersensitivity pneumonitis, hypersensitivity reaction, hypocalcemia, hypoesthesia, hypokalemia, hyponatremia, hypophosphatemia,

hypotension, hypoxia, intestinal obstruction, immunosuppression, increased blood urea nitrogen, increased creatinine clearance, increased gamma-glutamyl transferase, increased lactate dehydrogenase, increased serum alkaline phosphatase, infertility, infusion site reaction (erythema, inflammation, pain, pruritus, swelling, tenderness), inhibition of spermatogenesis, interstitial nephritis, interstitial pneumonitis, interstitial pulmonary disease, inversion T wave on ECG, irritable bladder, jaundice, left ventricular dysfunction (failure), leukoencephalopathy, limb pain, lymphocytopenia, malaise, mania, menopause (premature), mental status changes, metastases (including ALL, AML, APL, lymphoma, MDS, RCC, sarcomas, thyroid cancer), methemoglobinemia, mucosal inflammation, mucous membrane ulceration, multi-organ failure, muscle twitching, mutism, myalgia, myocardial infarction, myocarditis, nail disease, nephrogenic diabetes insipidus, neuralgia, neutropenia, oligospermia, oliguria, osteomalacia (adults), ovarian failure, pain, palmar-plantar erythrodysesthesia, pancreatitis, pancytopenia, panic attack, paranoia, parenchymal damage (renal), paresthesia, pericardial effusion, pericarditis, peripheral neuropathy, petechia, phosphaturia, physical health deterioration, pleural effusion, pneumonia (including *Pneumocystis jiroveci*), pneumonitis, pollakiuria, polydipsia, polyneuropathy, polyuria, portal vein thrombosis, progressive multifocal leukoencephalopathy, proteinuria, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, pulmonary hypertension, reduced ejection fraction, renal tubular acidosis, renal tubular necrosis, respiratory distress syndrome (acute), respiratory failure, reversible posterior leukoencephalopathy syndrome, rhabdomyolysis, rickets, salivation, seizure, sepsis, septic shock, SIADH, skin abnormalities related to radiation recall, skin necrosis, skin rash (including macular and papular), status epilepticus, sterility, Stevens-Johnson syndrome, stomatitis, ST segment changes on ECG, supraventricular extrasystole, tachycardia, talkativeness (logorrhea), tinnitus, toxic epidermal necrolysis, tumor lysis syndrome, typhlitis, uremia, urinary incontinence, urine abnormality (aminoaciduria and enzymuria), urticaria, vasculitis, ventricular fibrillation, ventricular premature contractions, ventricular tachycardia, vertigo, viral hepatitis, visual impairment, wound healing impairment

Contraindications

Known hypersensitivity to ifosfamide or any component of the formulation; urinary outflow obstruction

Canadian labeling: Additional contraindications (not in US labeling): Severe leukopenia/thrombocytopenia; severe renal and/or hepatic impairment; cystitis; active infection; advanced cerebral arteriosclerosis

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: **[US Boxed Warning]: Bone marrow suppression may occur (may be severe and lead to fatal infections); monitor blood counts before and after each cycle.** Leukopenia, neutropenia, thrombocytopenia, and anemia are associated with ifosfamide. Myelosuppression is dose dependent, increased with single high doses (compared to fractionated doses) and increased with decreased renal function. Severe myelosuppression may occur when administered in combination with other chemotherapy agents or radiation therapy. Use with caution in patients with compromised bone marrow reserve. Unless clinically necessary, avoid administering to patients with WBC <2,000/mm^3 and platelets <50,000/mm^3. Bleeding events due to thrombocytopenia may occur. Antimicrobial prophylaxis may be necessary in some neutropenic patients; administer antibiotics and/or antifungal agents for neutropenic fever.

• Cardiotoxicity: Ifosfamide-induced cardiotoxicity has been reported; may be fatal. Arrhythmias (eg, atrial/supraventricular tachycardia, atrial fibrillation, pulseless ventricular tachycardia), ST-segment or T-wave changes, cardiomyopathy, pericardial effusion, pericarditis, and epicardial fibrosis have been observed. The risk for cardiotoxicity is dose-dependent; concomitant cardiotoxic agents (eg, anthracyclines), irradiation of the cardiac region, and renal impairment may also increase the risk. Use with caution in patients with cardiac risk factors or pre-existing cardiac disease. In a scientific statement from the American Heart Association, ifosfamide has been determined to be an agent that may either cause reversible direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: moderate/major) (AHA [Page 2016]).

• CNS toxicity: **[US Boxed Warning]: May cause CNS toxicity which may be severe, resulting in encephalopathy and death; monitor for CNS toxicity; discontinue for encephalopathy.** Symptoms of CNS toxicity (somnolence, confusion, dizziness, disorientation, hallucinations, cranial nerve dysfunction, psychotic behavior, extrapyramidal symptoms, seizures, coma, peripheral neuropathy, blurred vision, and/or urinary incontinence) have been observed within a few hours to a few days after initial dose, and generally resolve within 2 to 3 days of treatment discontinuation (although symptoms may persist longer); maintain supportive care until complete resolution. Recurrence of CNS toxicity (after several cycles with no CNS incidents) has been reported. Risk factors for CNS toxicity may include hypoalbuminemia, renal dysfunction, and high-dose antiemetic therapy. Concomitant centrally-acting medications may result in additive CNS effects. Peripheral neuropathy has been reported.

• Gastrointestinal toxicity: Ifosfamide is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2010).

• Hemorrhagic cystitis: **[US Boxed Warning]: Hemorrhagic cystitis may occur (may be severe); concomitant mesna reduces the risk of hemorrhagic cystitis.** Hydration (at least 2 L/day in adults), dose fractionation, and/or mesna administration will reduce the incidence of hematuria and protect against hemorrhagic cystitis. Obtain urinalysis prior to each dose; if microscopic hematuria is detected, withhold until complete resolution. Exclude or correct urinary tract obstructions prior to treatment. Use with caution (if at all) in patients with active urinary tract infection. Hemorrhagic cystitis is dose-dependent and is increased with high single doses (compared with fractionated doses); past or concomitant bladder radiation or busulfan treatment may increase the risk for hemorrhagic cystitis.

• Hepatic effects: Hepatic sinusoidal obstruction syndrome (SOS), formerly called veno-occlusive disease (VOD), has been reported with ifosfamide-containing regimens.

• Hypersensitivity reactions: Anaphylactic/anaphylactoid reactions have been associated with ifosfamide. Cross sensitivity with similar agents may occur.

• Infection: May cause significant suppression of the immune responses; may lead to serious infection, sepsis or septic shock. Reported infections have included bacterial, viral, fungal, and parasitic; latent viral infections may be reactivated. Use with caution with other immunosuppressants or in patients with infection.

• Pulmonary toxicity: Interstitial pneumonitis, pulmonary fibrosis, and pulmonary toxicity leading to respiratory failure (may be fatal) have been reported. Monitor for signs and symptoms of pulmonary toxicity.

• Renal toxicity: **[US Boxed Warning]: May cause severe nephrotoxicity, resulting in renal**

failure. Nephrotoxicity may be fatal. Acute and chronic renal failure, as well as renal parenchymal and tubular necrosis (including acute), have been reported; tubular damage may be delayed (months to years) and may persist. Renal manifestations include decreased glomerular rate, increased creatinine, proteinuria, enzymuria, cylindruria, tubular acidosis, aminoaciduria, phosphaturia, and glycosuria. Syndrome of inappropriate antidiuretic hormone (SIADH), renal rickets, and Fanconi syndrome have been reported. Evaluate renal function prior to and during treatment; monitor urine for erythrocytes and signs of urotoxicity.

• Secondary malignancy: Secondary malignancies may occur (onset may be delayed); the risk for myelodysplastic syndrome (which may progress to acute leukemia) is increased with treatment.

• Wound healing: May interfere with wound healing.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Other warnings/precautions:

• Radiation therapy: Use with caution in patients with prior radiation therapy.

Metabolism/Transport Effects

Substrate of CYP2B6 (major), CYP2C19 (minor), CYP2C8 (minor), CYP2C9 (minor), CYP3A4 (minor); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Induces** CYP2C9 (weak/moderate)

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Aprepitant: May increase the serum concentration of Ifosfamide. Specifically, concentrations of the toxic metabolites of ifosfamide may increase. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Busulfan: May enhance the adverse/toxic effect of Ifosfamide. Specifically, the risk of hemorrhagic cystitis may be increased. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

CYP2B6 Inducers (Moderate): May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Moderate): May decrease serum concentrations of the active metabolite(s) of

Ifosfamide. CYP3A4 Inducers (Moderate) may increase serum concentrations of the active metabolite(s) of Ifosfamide. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May increase serum concentrations of the active metabolite(s) of Ifosfamide. CYP3A4 Inducers (Strong) may decrease serum concentrations of the active metabolite(s) of Ifosfamide. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Moderate): May decrease serum concentrations of the active metabolite(s) of Ifosfamide. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease serum concentrations of the active metabolite(s) of Ifosfamide. *Risk C: Monitor therapy*

Dabrafenib: May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of Ifosfamide. Specifically, concentrations of the toxic metabolites of ifosfamide may increase. *Risk C: Monitor therapy*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Lumacaftor: May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

MiFEPRIStone: May increase the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nilotinib: May decrease the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider*

therapy modification

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Thiotepa: May increase the serum concentration of CYP2B6 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Ifosfamide may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Pregnancy Risk Factor

D (show table)

Pregnancy Implications

Adverse effects have been observed in animal reproduction studies. Fetal

growth retardation and neonatal anemia have been reported with exposure to ifosfamide-containing regimens during human pregnancy. Male and female fertility may be affected (dose and duration dependent). Ifosfamide interferes with oogenesis and spermatogenesis; amenorrhea, azoospermia, and sterility have been reported and may be irreversible. Avoid pregnancy during treatment; male patients should not father a child during and for at least 6 months after completion of therapy.

Breast-Feeding Considerations Ifosfamide is excreted in breast milk. Breast-feeding is not recommended during ifosfamide treatment; due to the potential for serious adverse reactions in the breast-feeding infant, the manufacturer recommends a decision be made to discontinue ifosfamide or to discontinue breast-feeding, taking into account the benefits of treatment to the mother.

Monitoring Parameters CBC with differential (prior to each cycle and as clinically appropriate), urine output, urinalysis (prior to each dose), liver function, and renal function tests; signs and symptoms of neurotoxicity, pulmonary toxicity, and/or hemorrhagic cystitis

Mechanism of Action Causes cross-linking of strands of DNA by binding with nucleic acids and other intracellular structures, resulting in cell death; inhibits protein synthesis and DNA synthesis

Pharmacodynamics/Kinetics Pharmacokinetics are dose dependent

Distribution: V_d: Approximates total body water; penetrates CNS, but not in therapeutic levels

Protein binding: Negligible

Metabolism: Hepatic to active metabolites isofosforamide mustard, 4-hydroxy-ifosfamide, acrolein, and inactive dichloroethylated and carboxy metabolites; acrolein is the agent implicated in development of hemorrhagic cystitis

Half-life elimination (increased in the elderly):

High dose (3,800 to 5,000 mg/m^2): ~15 hours

Lower dose (1,600 to 2,400 mg/m^2): ~7 hours

Excretion:

High dose (5,000 mg/m^2): Urine (70% to 86%; 61% as unchanged drug)

Lower dose (1,600 to 2,400 mg/m^2): Urine (12% to 18% as unchanged drug)

Pricing: US

Solution (Ifosfamide Intravenous)

1 g/20 mL (20 mL): $69.60

3 g/60 mL (60 mL): $208.80

Solution (reconstituted) (Ifex Intravenous)

1 g (1): $79.66

3 g (1): $125.56

Solution (reconstituted) (Ifosfamide Intravenous)

1 g (1): $44.09

3 g (1): $129.05

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Alquimid (CR, DO, GT, HN, NI, PA, SV); Cuantil (AR, PY); Farmamide (DE); Fosfidex (CR, DO, GT, HN, NI, PA, SV); Holoksan (UA); Holoxan (AE, AT, AU, BD, BE, BG, BH, CH, CL, CN, CY, CZ, DE, DK, EC, EE, EG, FI, FR, GR, HK, HN, HR, HU, ID, IE, IL, IQ, IR, IS, IT, JO, KR, KW, LB, LT, LU, LV, LY, MT, MY, NL, NO, NZ, OM, PH, PK, PL, PT, QA, RO, RU, SA, SE, SG, SI, SK, SY, TH, TR, TW, UY, VN, YE); Holoxane (BR); Ifadex (CR, DO, GT, HN, MX, NI, PA, SV); Ifamide (BD); Ifolem (MX); Ifomida (MX); Ifomide (JP); Ifos (LB, PE, PY); Ipamide (IN); Iphox (PH); Mitoxana (GB); Tolcamin (CO); Tronoxal (ES); Xifox (BD)

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