DRUG NAME: Ifosfamide

SYNONYM(S): isophosphamide,[1] iphosphamide[2]

COMMON TRADE NAME(S): IFEX®

CLASSIFICATION: alkylating agent, cytotoxic[3]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Ifosfamide, like cyclophosphamide, is an oxazophosphorine alkylating agent. Following activation in the liver, ifosfamide interferes with DNA through formation of phosphotriesters and DNA-DNA crosslinks, thereby inhibiting protein synthesis and DNA synthesis.[1,4] Ifosfamide is cell cycle-specific, but cell cycle phase non-specific.[1,4] Ifosfamide is an immunosuppressive agent.[1,4]

PHARMACOKINETICS:

Oral Absorption	90-100%[1,5]; time to peak[5]: 1 hour	
Distribution	throughout the body	
	cross blood brain barrier?	yes[1], in sub-therapeutic amounts[5]
	volume of distribution[1,4,5]	6-49 L, slightly higher if obese[1]
	plasma protein binding	negligible[5]
Metabolism	activated by hepatic metabolism	
	active metabolite(s)	yes, including phosphoramide mustard and acrolein[5]
	inactive metabolite(s)	yes
Excretion	primarily renal	
	urine	14-50% as unchanged drug[1,4,5]; 15-41% other metabolites[1,4,5]
	feces	no information found
	terminal half life[1,4,5]	4-8 h; high dose (3,800-5,000mg/m^2) 11-15 h
	clearance[4]	21 mL/min
Elderly	small differences have been reported that are unlikely to be clinically relevant given interindividual variation	
Children	small differences have been reported that are unlikely to be clinically relevant given interindividual variation	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
Acute lymphoblastic leukemia L3 variant[6]
Brain tumours[1]
Burkitt's lymphoma[5]
Ewing's sarcoma[5]
Germ cell tumours[8] (gonadal, extra-gonadal, and non-seminomous)
Osteosarcoma[9,10]
Peripheral neuroectodermal tumour[5]
Rhabdomyosarcoma[1]
*Soft tissue sarcoma[1]

Other uses:
Bladder cancer[1]
Breast cancer[7]
*Cervical cancer
Chronic lymphocytic leukemia[6]
Gastric cancer[5]
Germ cell testicular cancer[5]
Lung cancer[8]
Lymphoma, Hodgkin's[8]
Lymphoma, non-Hodgkin's[1]

Ovarian cancer[11]
*Pancreatic cancer

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindicated in patients having severe leukopenia, thrombocytopenia, severe renal and/or hepatic impairment, cystitis, obstructions to urine flow, active infections, or advanced cerebral arteriosclerosis.[5]

Renal and bladder toxicity:
- A uroprotective agent such as mesna must be used[5]; see paragraph following **Side Effects** table.
- Rule out or correct any obstruction or infection of the urinary tract before initiating treatment.[8,12]
- Rule out or correct any electrolyte imbalances before initiating treatment.[1]
- Do not administer within three months of a unilateral nephrectomy.[1]
- Use caution in all patients with unilateral nephrectomy or impaired renal function
- Use caution in patients with prior or concomitant use of nephrotoxic drugs.[4]
- Daily fluid intake must be at least 2 liters.
- If urinary excretion is insufficient, a fast-acting diuretic such as furosemide may be administered.[4]

Impaired wound healing is a possibility. Do not initiate treatment for at least 10 to 14 days after surgery.[4]

Caution in patients with[4]:
- tumour infiltration of the bone marrow
- prior radiation therapy
- brain metastases and advanced cerebral arteriosclerosis
- impaired hepatic function
- abnormal serum albumin levels

Special populations: Ifosfamide has been used in **children**, but safety and efficacy have not been established. Adverse effects appear similar to those reported in adults.[4] Those 5 years of age or younger may be more susceptible to renal toxicity than older children or adults. Severe nephrotoxicity leading to Fanconi's syndrome, which may be irreversible, has been reported in young children who received ifosfamide alone or in conjunction with other antineoplastic agents. Some clinicians recommend that ifosfamide not be used in children with infiltrating renal tumours, prior nephrectomy, or any evidence of renal impairment.

Carcinogenicity: Oncogenic in animals.[4] Carcinogenic in rats.[4]

Mutagenicity: Mutagenic *in vitro* in bacterial systems, in mammalian *in vivo* mutation test, and in *Drosophila in vivo* mutation test.[1,4] Adequate methods of contraception are recommended for male and female patients, due to mutagenic potential.[4]

Fertility: Effect on fertility not fully determined.[4] Gonadal suppression, resulting in amenorrhea or azoospermia, has been reported with structurally similar drugs and thus may occur.[4]

Pregnancy: FDA Pregnancy Category D.[1] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended as the drug is distributed into breast milk.[1] Breastfeeding should be discontinued prior to institution of therapy.[4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[1] When placebo-controlled trials are available, adverse events are included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic reactions (<1%)[4]
auditory/hearing	auditory hallucinations[5]
blood/bone marrow/ febrile neutropenia	anemia
	leukopenia, 6,000 mg/m^2/cycle (50%)[1]; 10,000-12,000 mg/m^2/cycle (~100%, severe 50%)[4]; begins around day 5,[13] nadir 7-14 days,[1] recovery begins after 10-14 days and is complete after 14-21 days[1]
	thrombocytopenia (10%)[1], 6,000 mg/m^2/cycle (20%)[1]; 10,000-12,000 mg/m^2/cycle (severe 8%)[4]
cardiovascular (arrhythmia)	S-T segment changes
	supraventricular arrhythmias
	ventricular arrhythmias
cardiovascular (general)	heart failure
constitutional symptoms	fever of unknown origin (1%)[1,4]
dermatology/skin	*extravasation hazard: irritant*[4]
	alopecia (1-83%)[5]
	dermatitis
	hyperpigmentation[1]
	inflammation of mucous membranes
gastrointestinal	*emetogenic potential: low-moderate; dose-related*[1]
	hematemesis
	nausea and/or vomiting (56-81%)[1]
hemorrhage	hematemesis
	hemorrhagic cystitis (1-10%)[1]; incidence, severity, and persistence increase with increased dose
	petechial bleeding
hepatobiliary/pancreas	pancreatitis (<1%)[1,4]
infection	infection with or without fever (8%)[1]; see paragraph following **Side Effects** table
metabolic/laboratory	hyperaminoaciduria
	increased liver enzymes and/or bilirubin (3%)[14]
	increased serum creatinine

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	metabolic acidosis (31%)
	phosphaturia
musculoskeletal	asthenia
neurology (see paragraph following **Side Effects** table)	agitation[1]
	cerebellar symptoms
	coma
	cranial nerve dysfunction
	depressive psychosis
	encephalitis (<1%)
	encephalopathy (10-50%)[4]; including confusion, disorientation, dizziness, somnolence, stupor[1]
	generalized seizures (<1%)
	hallucinations
	mutism[1]
	peripheral neuropathy (<1%)[1]
	polyneuropathy (<1%)[1]
	seizure
ocular/visual	impaired or blurred vision
pulmonary	interstitial pneumonitis (<1%)
	pulmonary edema (<1%)
renal/genitourinary	cylindruria
	dysuria
	hematuria (6-92%)[15,16]; 6 g/m^2/cycle (microscopic 50%, gross 8%)[1]; typically would occur on day of treatment,[1] and resolves spontaneously upon cessation of ifosfamide therapy[1]; see paragraph following **Side Effects** table
	hemorrhagic cystitis (1-10%); incidence, severity, and persistence increase with increased dose; see paragraph following **Side Effects** table
	nephrogenic diabetes insipidus[1]
	proteinuria
	renal failure (<1%)[1]
	renal parenchymal necrosis
	renal rickets
	renal tubular acidosis
	renal tubular necrosis
	unspecified nephrotoxicity (6%)[1]
	urinary frequency, incontinence, and retention
sexual/reproductive function	gonadal suppression (amenorrhea or azoospermia)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
syndromes	Fanconi syndrome
vascular	thrombophlebitis (1%)[13]

Adapted from standard reference[4] unless specified otherwise.

Neurotoxicity: Ifosfamide-induced encephalopathy is reported in 10-50% of patients.[1] Most cases are reversible.[1] Symptoms can appear one to four days after administration and may persist from one to thirty days.[1] Numerous non-specific symptoms[1] have been reported including:

- extrapyramidal symptoms,
- fecal and/or urinary incontinence,
- seizures,
- somnolence, confusion, amnesia, and
- depressive psychosis, hallucinations, and other psychiatric disturbances.

The clinical picture can range in severity from mild somnolence or agitation to hallucinations to deep coma.[4] Fatalities have been reported.[15,16] Occasionally, encephalopathy is persistent with chronic neurologic disturbances.[15,17] Encephalopathy may be dose-dependent.[15] It is more common after oral treatments and, when given intravenously, risk is increased by short infusion times.[15] Other suggested risk factors include: renal and liver dysfunction, low serum albumin, poor performance status, prior CNS disease, pelvic disease, prior cisplatin treatment, prior CNS irradiation, female gender, and age greater than 65 years.[18,19] Close monitoring of neurologic status and renal function is suggested to enable early detection and treatment of neurotoxicity.[15,17] If acute neurotoxicity occurs, discontinue ifosfamide and institute appropriate supportive therapy. Methylene blue may be effective for the treatment and prophylaxis of encephalopathy.[15,17]

Urotoxicity: To decrease the incidence and severity of bladder toxicity, use conventional uroprophylaxis (e.g., adequate hydration, maintenance of fluid balance, frequent urination) and mesna, a uroprotective agent. These measures do not prevent hemorrhagic cystitis in all patients and urine should be examined regularly for erythrocytes, the appearance of which may precede hemorrhagic cystitis. A morning urine specimen should be examined before each scheduled dose of ifosfamide. In patients who develop microscopic hematuria, ifosfamide therapy should be discontinued until the hematuria resolves. Vigorous oral or parenteral hydration as well as mesna should be used for subsequent courses of ifosfamide. Hemorrhagic cystitis can be severe and may be fatal. Therefore, ifosfamide should be discontinued or dose reduced in patients who develop hematuria despite concurrent use of mesna.[15-17]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
warfarin[15,18]	anticoagulant effect of warfarin may be enhanced	unknown	monitor for bleeding; reduce warfarin dose as necessary

Ifosfamide is a major substrate of CYP3A4.[15-17,20] CYP3A4 inducers may increase the serum levels/effects of acrolein. CYP3A4 inhibitors may decrease the serum levels/effects of acrolein.

Ifosfamide is a minor substrate of CYP2A6, 2B6, 2C8, 2C9, 2C19.[15,16]

Ifosfamide is a weak inhibitor of CYP3A4.[1,15,17,18,21,22]

Ifosfamide is a weak inducer of CYP2C8, 2C9.[1]

SUPPLY AND STORAGE:

Injection: Baxter supplies ifosfamide sterile powder in 1 g and 3 g vials.[4,23]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***over 60-120 minutes***[5] over a minimum of 30 minutes[5]
Continuous infusion[5]	***over 24 hours***[5]
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
**Intravenous:*	3 weeks[4]:	1,200 mg/m^2 IV once daily for 5 consecutive days starting on day 1 (total dose per cycle 6000 mg/m^2)
	based on response[5,6,8-10]:	1,200-2,500 mg/m^2 IV once daily for 3-5 days starting on day 1
	3 weeks[4]:	***1,500-1,800 mg/m^2 IV once daily for 4-5 consecutive days starting on day 1 (total dose per cycle 6000-9000 mg/m^2)***
	3 weeks[1]:	***5,000 mg/m^2 IV once daily for one dose on day 1***

3-4 weeks[1]:	5,000-8,000 mg/m^2 IV once daily for one dose on day 1
3-4 weeks[7,12]:	50-60 mg/kg IV once daily for 5 consecutive days starting on day 1 (total dose per cycle range: 250-300 mg/kg, or 2,000-2,400 mg/m^2) May be given every other day or for 10 consecutive days if a lower dose or longer duration is required.

*Ifosfamide should not be administered without the use of a uroprotective agent such as mesna.[1]
See mesna monograph or refer to treatment protocol.

Concurrent radiation: ifosfamide has been reported to cause increased sensitivity to radiation[1]

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: modify according to protocol[6,8-10]; otherwise, refer to table below[7,12]:

Creatinine Clearance (mL/min)	Dose
≥10	100%
<10	75%

$$\text{Calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{Weight in kg}}{\text{Serum Creatinine in } \mu\text{mol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: adjustment may be required[4]

Dosage in dialysis: no information found

Children:

Intravenous: refer to treatment protocol

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