Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

ifosfamide

SYNONYM(S): IFO; Iphosphamide; Isophosphamide; NSC-109724

COMMON TRADE NAME(S): Ifex® (Baxter)

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B - Mechanism of Action and Pharmacokinetics

Ifosfamide is a structural analogue of cyclophosphamide and its mechanism of action is presumed to be identical. Ifosfamide is cell cycle phase-nonspecific. Cross-resistance has been reported in vitro between ifosfamide, cyclophosphamide and other alkylating agents.

Absorption	Oral: 90-100% bioavailability, but associated with significant neurotoxicity IV: Maximal concentration of alkylating metabolites occurred at 3 hours after dosage	
Distribution	Distributed throughout the body. Present in breast milk and in ascites.	
	Cross blood brain barrier?	Ifosfamide: yes, low; active metabolites: no
	PPB	low
Metabolism	Activated by hepatic microsomal enzyme oxidation system; pathways saturated at higher doses; autoinduction of hepatic metabolism → time dependent decrease of half-life	
	Active metabolites	Ifosfamide mustard, acrolein
	Inactive metabolites	yes

Elimination	Excreted in kidneys; elimination fits two compartment model for large bolus doses and one compartment model for fractionated doses.	
	Urine	± 50% unchanged, 20-36% as metabolites
	Half-life	7-15 hrs (depending on schedule)

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C - Indications and Status

Health Canada Approvals:

- Cervical cancer (single agent or combination, advanced or recurrent disease)
- Sarcoma, soft tissue (single agent, 1st or 2nd line)
- Pancreatic cancer (single agent, 2nd line)

Other Uses:

- Genitourinary cancer (penile, testicular)
- Sarcomas (osteogenic, Ewing's, uterine)
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Germ cell ovarian cancer

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: Irritant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Auditory	Tinnitus / deafness (rare)	E D
Cardiovascular	Arrhythmia (rare, at high doses)	E
	Arterial thromboembolism (rare)	E
	Cardiotoxicity (<1%, at high doses)	E

	Hypotension (<1%)	E
	Venous thromboembolism (rare)	E
Dermatological	Alopecia (90%)	E
	Rash (<1%, may be severe)	E
Gastrointestinal	Abdominal pain (rare)	E
	Anorexia (1%)	E
	Constipation (rare)	E
	Diarrhea (<1%)	E
	Mucositis (<1%)	E
	Nausea, vomiting (47%)	I
General	Edema (including effusions)	E
	Fatigue (<1%)	E
Hematological	Disseminated intravascular coagulation (rare)	E
	Hemolysis (rare)	E
	Hemolytic uremic syndrome (rare)	E
	Immunosuppression	E
	Myelosuppression ± infection, bleeding (grade 3 or 4: 44%)	E
Hepatobiliary	↑ LFTs (2%) (may be severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (rare)	I
Injection site	Phlebitis (3%)	I
Metabolic / Endocrine	Abnormal electrolyte(s)	E
	Acidosis (rare)	E
	SIADH (rare)	I E
Musculoskeletal	Arthralgia / myalgia	E
	Rhabdomyolysis (rare)	E
Neoplastic	Secondary malignancy (rare)	D L
Nervous System	Neuropathy (peripheral, <1%)	E
	Neurotoxicity (15%)	I E
	Vertigo (rare)	E
Ophthalmic	Blurred vision (rare)	E
	Conjunctivitis	E
Renal	Nephrotoxicity (>10%)	E

	Renal tubular acidosis (>10%, proximal tubular damage, Fanconi syndrome)	E D L
Reproductive and breast disorders	Infertility (gonadal damage)	L
Respiratory	Pneumonitis (rare)	D
Urinary	Hemorrhagic Cystitis (21%)	I E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common reported side effects are **alopecia, nausea and vomiting, hemorrhagic cystitis, nephrotoxicity** and **myelosuppression**.

The incidence of **urotoxic effects** without an uroprotector can be up to 40% and is dose-dependent; coadministration with mesna and adequate hydration are mandatory. Patients may present with hematuria, symptomatic cystitis or bladder fibrosis. Past or concomitant radiation of the bladder or busulfan treatment may increase the risk of hemorrhagic cystitis. Several methods of treatment for established hematuria have been described: Bladder irrigation with water or NS, intravesical instillation of astringents (alum, silver nitrate), systemic administration of antifibrinolytics (aminocaproic acid, tranexamic acid), cystoscopy to evacuate the bladder of clots, continuous bladder irrigation and intravesical prostaglandins. For severe or refractory hematuria**,** intravesical formalin, phenol or prostaglandin has been used ± surgical intervention (electrocautery, cryosurgery, diversion of urine flow, hypogastric artery ligation or cystectomy).

Glomerular, proximal or distal tubular impairment may all occur, often in combination and may progress even after ifosfamide has been discontinued. **Proximal tubular damage** often presents as Fanconi syndrome with low serum bicarbonate, proteinuria, glucosuria, aminoaciduria and hypochloremic metabolic acidosis. Risk factors for the development of nephrotoxicity include age less than 5 years; pre-existing renal impairment; prior treatment with cisplatin; concurrent use of nephrotoxic drugs, reduced renal reserve (unilateral nephrectomy, renal radiation); hydronephrosis and total cumulative dose. Renal impairment may increase the risk of myelosuppression and possibly, cardiotoxicity. Mesna does not appear to be protective against the proximal tubular abnormalities induced by ifosfamide.

Central nervous system toxicity appears to be dose-dependent, and is variable in onset, but usually resolve when ifosfamide is discontinued. Incidence is higher with higher doses, concomitant use of aprepitant, electrolyte imbalances, renal/ hepatic impairment or pre-existing CNS disorders. It may manifest as transient mental status changes (somnolence, confusion, hallucination, disorientation, and lethargy), cerebellar dysfunction, extrapyramidal symptoms, transient weakness, cranial nerve dysfunction or seizure activity. Methylene blue, which may act as an electron acceptor or decrease chloracetaldehyde formation, has been suggested as treatment or prophylaxis of ifosfamide-induced encephalopathy.

Myelosuppression is dose and AUC-dependent.

Arrhythmia, ST- and T-wave changes, cardiomyopathy, effusions and pericardial fibrosis have been reported. **Cardiac effects** are dose dependent and the risk is increased with known cardiac risk factors.

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E - Dosing

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 white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

Electrolyte imbalances, urinary obstruction and cystitis must be excluded before treatment and adequate hydration is needed. The use of concurrent mesna is mandatory to prevent severe hematuria from ifosfamide. For ifosfamide short infusions, mesna (at 20% of the ifosfamide dose for each dose of mesna) should be given IV at the start plus at 4 and 8 hours after each ifosfamide dose. See mesna drug monograph.

Prophylactic anti-emetics are required; the risk of neurotoxicity is increased with concomitant use of aprepitant.

Adults:

Single agent (q3-4 weeks):

- IV short infusion: 2 to 2.4 g/m^2 per day on 5 consecutive days
- IV continuous infusion: 5-8 g/m^2 total dose over 24 hours with continuous mesna infusion

Dosage with Toxicity:

Dosage in myelosuppression:
Modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Hematologic and Non-Hematologic Toxicities."

(Continued on next page)

Worst Toxicity / Counts (x 10^9/L) in previous cycle		**Worst Toxicity / Counts (x 10^9/L) in previous cycle**	**Ifosfamide (% previous dose)***
Febrile Neutropenia Or ANC < 0.5 for ≥ 5-7 days	Or	Thrombocytopenic bleeding Or Platelets < 25	↓ 20% or consider GCSF for isolated neutropenia
ANC ≥ 1.5	Or	Platelets ≥ 100	100%
Somnolence or other signs of encephalopathy			Hold; methylene blue 50mg IV q4h until resolution. Consider prophylactic methylene blue for subsequent cycles. Consider discontinuing or dose reduction for next cycle.
Grade 3 or 4 neurotoxicity			Discontinue
Grade 3 related organ / non-hematologic			↓ 20%
Grade 4 related organ / non-hematologic LVEF ≤ 45%			Discontinue
* Do not retreat until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and toxicity recovered to ≤ grade 2.			

Management of Urotoxicity

Finding	Action
Microscopic hematuria	Hold ifosfamide until resolves
Macroscopic hematuria	Discontinue or reduce dose

Dosage with Hepatic Impairment:

Suggested:

Bilirubin		AST/ALT	Ifosfamide* (% previous dose)
1-2 x ULN	and/ or	<2 x ULN	100%
2-4 x ULN		2-5 x ULN	75%
> 4 x ULN		> 5 x ULN	Discontinue

*Based on clinical judgment – less conservative adjustments can be considered if hepatic changes are secondary to metastases rather than hepatic cirrhosis or hepatitis.

Dosage with Renal Impairment:

Suggested:

Creatinine Clearance (mL/min)	Ifosfamide (% previous dose)
> 60	100%
40-60	75%
20-40	50%
< 20	Discontinue

Dosage in the elderly:

Exercise caution as the elderly population may have decreased hepatic, renal, cardiac or hematopoietic function. Increased in half-life has been observed with advancing age; however, no significant changes in clearance were reported.

Children:

Safety and efficacy have not been established in registrational trials. Refer to treatment protocol for details. Side effects in children were reported to be similar to those in adults. Children 5 years of age or younger may be more susceptible to ifosfamide- induced renal toxicity than older children and adults.

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F - Administration Guidelines

- May give bolus dose of mesna before ifosfamide infusion, with or without mesna admixed in ifosfamide solution, then followed by 2 doses of mesna by IV bolus or PO, see mesna monograph.
- Add reconstituted drug to NS or D5W for infusion; the final concentration should be between 0.6 to 20 mg/mL.
- May mix doses ≤2000mg in 100mL bag; Infuse over 30-60 minutes.

- May mix doses >2000mg in 500-1000mL bag; Infuse over 1-4 hours.
- May be admixed with mesna.
- Oral hydration is strongly encouraged; poorly hydrated patients may need more IV hydration.
- Inadequate total hydration may result in dose-related hemorrhagic cystitis.

IFOSFAMIDE AND MESNA INFUSION ADMIXTURE

- May be diluted in larger volumes for continuous infusion over 6-24 hours; May be infused using a CADD ambulatory infusion pump over longer periods.

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G - Special Precautions

Other:

Ifosfamide is **contraindicated** in patients with known hypersensitivity to the drug, with severe myelosuppression, severe renal and/or hepatic impairment, cystitis, obstructive uropathy, active infections/severe immunosuppression, or cerebral arteriosclerosis.

Mesna must be coadministered. Use with caution in patients with prior radiotherapy or anticancer therapy, concomitant aprepitant usage, hepatic or renal impairment, risk factors for cardiotoxicity, hypoalbuminemia, pre-existing cardiac disease, brain or extensive bone marrow metastases, concurrent or prior use of nephrotoxic agents or prior nephrectomy. Do not use within 10 to 14 days of surgery or within 3 months after nephrectomy. Avoid the use of live vaccines. Electrolytes imbalances must be corrected before treatment. CNS effects may interfere with driving or tasks that require alertness.

Ifosfamide has **mutagenic, teratogenic, fetotoxic and carcinogenic** properties and should not be used in **pregnancy**. Effective contraception must be used by both sexes during ifosfamide treatment and for at least **12 months** after treatment cessation. **Fertility** is usually affected. In post-pubertal boys ifosfamide may cause irreversible gonadal damage resulting in sterility. Ifosfamide is excreted in **breast milk**, therefore breastfeeding is not recommended.

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H - Interactions

Ifosfamide is a major substrate of CYP3A4 and a minor substrate of 2A6, 2B6, 2C8, 2C19 and 2C9. Inhibitors or inducers of these isoenzymes may decrease or increase the metabolism of ifosfamide. Ifosfamide is also a weak inhibitor of CYP3A4 and a weak inducer of CYP2C8 and 2C9. Patients receiving agents that reduce ifosfamide activation should be monitored for a possible reduction in therapeutic effectiveness; dosage adjustment may be required.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Aprepitant	↑ neurotoxicity reported; may ↓ effectiveness of ifosfamide	inhibits ifosfamide metabolism and → formation of neuro/nephrotoxic metabolites	Caution and monitor
Drugs acting on the CNS (e.g. antihistamines, narcotics, some antiemetics, sedatives, SSRIs, neuroleptics, tricyclics)	↑ CNS toxicity	Additive	Discontinue if possible. Caution and monitor for CNS toxicity if must be used.
Hepatic-enzyme inducing drugs (e.g. phenytoin, phenobarbital, corticosteroids, St. John's wort)	May ↑ ifosfamide toxicity	↑ activation of ifosfamide to its active and toxic metabolite	Caution and monitor
radiation	May ↑ sensitivity to radiation; ↑ hemorrhagic cystitis (radiation of bladder), ↑ cardiotoxicity (radiation of cardiac region)	Additive	Caution and monitor
warfarin	↑ anti-coagulant effect, ↑ INR	possibly inhibition of warfarin metabolism and/or displacement of warfarin from protein binding sites	monitor prothrombin time
Docetaxel	↑ GI toxicity when ifosfamide given before docetaxel infusion	Unknown	Avoid; monitor closely if must be used
CYP3A4 inhibitors (i.e. ketoconazole, voriconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges, starfruit or pomegranate)	May ↓ ifosfamide effectiveness, or ↑ formation of neurotoxic metabolite through another metabolic pathway	↓ activation and metabolism of ifosfamide	Caution and monitor
Cisplatin	↑ hearing loss,	Unknown (hearing	Caution and monitor

	nephrotoxicity	loss); additive (nephrotoxicity)	
Alcohol	↑ nausea/vomiting or neurotoxicity	Additive	Avoid
ACE inhibitors	↑ risk of leukopenia or agranulocytosis	Additive	Caution and monitor
Other cardiotoxic drugs (anthracyclines)	↑ cardiotoxicity risk	Additive	Caution and monitor
Other nephrotoxic drugs (e.g. cisplatin, aminoglycosides, amphotericin B, acyclovir)	↑ risk of nephrotoxicity	Additive	Caution and monitor
Busulfan	↑ risk of hemorrhagic cystitis	Additive	Caution and monitor
Immunosuppressants	↑ immuno-suppression	Additive	Caution and monitor
Drugs that may cause pulmonary toxicity (e.g. amiodarone, bleomycin)	↑ risk of lung toxicity	Additive	Caution and monitor

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and regular
Urinalysis, for RBCs and specific gravity	before each dose and regular
Liver function tests	Baseline and regular
Renal function tests, including electrolytes	Baseline and regular
Clinical assessment of neurotoxicity (especially in patients with increased risk), infection, bleeding and cystitis	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

Ajithkumar T, Parkinson C, Shamshad F, et al. Ifosfamide encephalopathy. Clinical Oncology 2006; 19: 108-14.

Chang TKH, Weber GF, Crespi CL, et al. Differential activation of cyclophosphamide and ifosphamide by cytochromes P-450 2B and 3A in human liver microsomes. Cancer Research 1993;53:5629-37.

Chang TKH. Cytochrome P450 in cancer therapeutics. In: Ioannides C, ed. Cytochromes P450: role in the metabolism and toxicity of drugs and other xenobiotics. Guildford, UK: Royal Society of Chemistry; 2008, p. 485.

DeVries CR, Freiha FS. Hemorrhagic cystitis: a review. J Urology 1990; 143(1): 1-9.

Ifosfamide: The Merck Manual [Internet]; 2011 [cited 2012 March 12]. Available from: http://www.merckmanuals.com/professional/lexicomp/ifosfamide.html

Jarkowski A 3rd. Possible contribution of aprepitant to ifosfamide-induced neurotoxicity. Am J Health Syst Pharm. 2008 Dec 1;65(23):2229-31.

Lokiec F. Ifosfamide: pharmacokinetic properties for central nervous system metastasis prevention. Ann Oncol 2006; 17 (Suppl 4): iv33–6.

Lorigan P, Verweij J, Papai Z, et al. Phase III trial of two investigational schedules of ifosfamide compared with standard-dose doxorubicin in advanced or metastatic soft tissue sarcoma: a European Organisation for Research and Treatment of Cancer soft tissue and bone sarcoma group study. J Clin Oncol 2007;25:3144-50.

McEvoy GK, editor. AHFS Drug Information 2011. Bethesda: American Society of Health-System Pharmacists, p. 1093-8.

Product monograph: Ifex® (ifosfamide). Baxter Corporation, April 5, 2012.

Sarosy G. Ifosfamide – pharmacologic overview. Semin Oncol 1989; 16(1 Suppl 3): 2-8.

August 2016 edited other indications

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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