

Ifosfamide

Class: Alkylating agent

Indications:

- _ (third-line) of germ cell testicular cancer
- _ pancreatic cancer (relapsed or refractory)
- _ cervical cancer
- _ bladder cancer (metastatic)
- _ small cell lung cancer (relapsed)
- _ Hodgkin lymphoma (relapsed or refractory)
- _ non-Hodgkin lymphomas

Available dosage form in the hospital: 1 G, 2 G VIAL

Trade name: Ifex

Doses: Also consult details concerning dosing in combination regimens. **Note:** To prevent bladder toxicity, ifosfamide should be given with the urinary protector mesna and hydration of at least 2 L of oral or I.V. fluid per day.

-Testicular cancer: I.V.:

- U.S. manufacturer's labeling; as part of combination chemotherapy and with mesna: 1200 mg/m²/day for 5 days every 3 weeks or after hematologic recovery
- VIP regimen: 1200 mg/m²/day for 5 days every 3 weeks for 4 cycles (in combination with etoposide, mesna, and cisplatin)
- VeIP regimen: 1200 mg/m²/day for 5 days every 3 weeks for 4 cycles (in combination with vinblastine, mesna, and cisplatin)

-Canadian labeling: Soft tissue sarcoma, cervical cancer (advanced or recurrent), pancreatic cancer (relapsed or refractory): I.V.: 2000-2400 mg/m²/day for 5 consecutive days (with mesna), may repeat after 3-4 weeks (or longer depending on patient status) or if lower daily dosage or total dosage over a longer time period is indicated, administer every other day (eg, days 1, 3, 5, 7, 9) or over 10 consecutive days at reduced doses.

High **single-dose infusions of up to 5000-8000 mg/m²/24 hour with continuous mesna may also be feasible; may repeat after 3-4 weeks (or longer depending on patient's condition).

-Adult unlabeled uses and/or dosing:

-Testicular cancer: I.V.:

- TIP regimen (unlabeled dosing): 1500 mg/m²/day for 4 days (days 2-5) every 3 weeks for 4 cycles (in combination with paclitaxel, mesna, and cisplatin)

-TICE regimen (unlabeled dosing): 2000 mg/m²/day for 3 days (days 2-4) over 4 hours every 2 weeks for 2 cycles (in combination with paclitaxel and mesna; followed by carboplatin and etoposide)

-Cervical cancer, recurrent or metastatic: I.V.: 1500 mg/m²/day for 5 days every 3 weeks (with mesna)

-Hodgkin lymphoma, relapsed or refractory: I.V.:

-ICE regimen: 5000 mg/m² (over 24 hours) beginning on day 2 every 2 weeks for 2 cycles (in combination with mesna, carboplatin, and etoposide)

-IGEV regimen: 2000 mg/m²/day for 4 days every 3 weeks for 4 cycles (in combination with mesna, gemcitabine, vinorelbine, and prednisolone)

-MINE-ESHAP regimen: 1500 mg/m²/day for 3 days every 4 weeks for up to 2 cycles (MINE is combination with mesna, mitoxantrone, and etoposide; MINE alternates with ESHAP for up to 2 cycles of each)

-Non-Hodgkin lymphomas: I.V.:

-CODOX-M/IVAC regimen:

-Adults ≤65 years: Cycles 2 and 4 (IVAC): 1500 mg/m²/day for 5 days (IVAC is combination with cytarabine, mesna, and etoposide; IVAC alternates with CODOX-M)

-Adults >65 years: Cycles 2 and 4 (IVAC): 1000 mg/m²/day for 5 days (IVAC is combination with cytarabine, mesna, and etoposide; IVAC alternates with CODOX-M)

-MINE-ESHAP regimen: 1330 mg/m²/day for 3 days every 3 weeks for 6 cycles (MINE is combination with mesna, mitoxantrone, and etoposide; followed by ESHAP)

-RICE regimen: 5000 mg/m² (over 24 hours) beginning on day 4 every 2 weeks for 3 cycles (in combination with mesna, carboplatin, etoposide, and rituximab)

-Ewing sarcoma: I.V.:

-VAC/IE regimen: Adults ≤30 years: IE: 1800 mg/m²/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

-VAIA regimen: 3000 mg/m²/day on days 1, 2, 22, 23, 43, and 44 for 4 courses (in combination with vincristine, doxorubicin, dactinomycin, and mesna) **or** Adults ≤35 years: 2000 mg/m²/day for 3 days every 3 weeks for 14 courses (in combination with vincristine, doxorubicin, dactinomycin, and mesna)

-VIDE regimen: Adults ≤50 years: 3000 mg/m²/day over 1-3 hours for 3 days every 3 weeks for 6 courses (in combination with vincristine, doxorubicin, etoposide, and mesna)

-IE regimen: 1800 mg/m²/day over 1 hour for 5 days every 3 weeks for 12 cycles (in combination with etoposide and mesna)

-ICE regimen: Adults ≤22 years: 1800 mg/m²/day for 5 days every 3 weeks for up to 12 cycles (in combination with carboplatin and etoposide [and mesna])

-Osteosarcoma: I.V.:

- Ifosfamide/cisplatin/doxorubicin/HDMT regimen: Adults <40 years: 3000 mg/m²/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)
- Ifosfamide/cisplatin/epirubicin regimen: 2000 mg/m²/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)
- ICE regimen (adults ≤22 years): 1800 mg/m²/day for 5 days every 3 weeks for up to 12 cycles (in combination with carboplatin and etoposide [and mesna])

-Soft tissue sarcoma: I.V.:

- Single-agent ifosfamide: 3000 mg/m²/day over 4 hours for 3 days every 3 weeks for at least 2 cycles or until disease progression
- ICE regimen: 1500 mg/m²/day for 4 days every 4 weeks for 4-6 cycles (in combination with carboplatin, etoposide, and regional hyperthermia)
- MAID regimen: 2000 mg/m²/day continuous infusion for 3 days every 3 weeks (in combination with mesna, doxorubicin, and dacarbazine) **or** 2500 mg/m²/day continuous infusion for 3 days every 3 weeks (in combination with mesna, doxorubicin, and dacarbazine); reduce ifosfamide to 1500mg/m²/day if prior pelvic irradiation
- Ifosfamide/epirubicin: 1800 mg/m²/day over 1 hour for 5 days every 3 weeks for 5 cycles (in combination with mesna and epirubicin)
- AIM regimens: 1500 mg/m²/day over 2 hours for 4 days every 3 weeks for 4-6 cycles (in combination with mesna and doxorubicin) or 2000-3000 mg/m²/day over 3 hours for 3 days (in combination with mesna and doxorubicin).

Geriatric

Refer to adult dosing.

Renal Impairment:

-*U.S. labeling:* Consider dosage reduction in patients with renal impairment; however, no dosage adjustment is 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.

-*Canadian labeling:*

-Mild-to-moderate impairment: No dosage adjustment provided in the manufacturer's labeling.

-Severe impairment: Use is contraindicated.

**The following adjustments have also been recommended:

-Aronoff, 2007:

- $Cl_{cr} \geq 10$ mL/minute: No dosage adjustment necessary.
- $Cl_{cr} < 10$ mL/minute: Administer 75% of dose.

- Hemodialysis (supplement for dialysis): No supplemental dose needed
- Kintzel, 1995:
- Cl_{cr} 46-60 mL/minute: Administer 80% of dose
 - Cl_{cr} 31-45 mL/minute: Administer 75% of dose
 - Cl_{cr} <30 mL/minute: Administer 70% of dose

Hepatic Impairment:

No dosage adjustment 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.

Canadian labeling:

- Mild-to-moderate impairment: No dosage adjustment provided in manufacturer labeling; use with caution.
- Severe impairment: Use is contraindicated.

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).

Common side effect :

Central nervous system: CNS toxicity or encephalopathy (12% to 15%)

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

Endocrine & metabolic: Metabolic acidosis (31%)

Gastrointestinal: Nausea/vomiting (47% to 58%)

Hematologic: Leukopenia (50% to \leq 100%)

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

Pregnancy category : D