Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

IFOS Regimen

Ifosfamide

Disease Site	Sarcoma - Osteogenic / Bone Sarcoma - Soft Tissue
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Additional Information	Sarcomas are rare tumours and as such benefit from referral to specialized centres where there will be access to multidisciplinary expertise including good radiology, orthopedic and thoracic surgery, medical oncology, radiation oncology, pathology, and other supportive care disciplines.

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B - Drug Regimen

Multiple regimens exist with various dosing schedules, an option would be:

ifosfamide	1500 mg/m2 to 3000 mg /m²	IV	Days 1 to 3
mesna			

Evidence-based mesna dosing can be variable, an option would be:

- mesna (20% of ifosfamide dose) IV pre-ifosfamide, and then
- mesna (40% of ifosfamide dose) PO 4 and 8 hours after ifosfamide

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

- Use standard alkalinization / hydration regimens for ifosfamide.
- Inadequate total hydration may result in dose-related hemorrhagic cystitis.

Also refer to CCO Antiemetic Summary

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

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."

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

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.

Renal Impairment

Suggested:

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

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F - Adverse Effects

Refer to ifosfamide, mesna drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Alopecia • Nausea, vomiting • Abdominal pain • Dysgeusia (oral mesna) • Hemorrhagic cystitis (may be severe) • Neurotoxicity (may be severe) • Diarrhea • Flu-like symptoms • Nephrotoxicity (may be severe) • Myelosuppression +/- infection, bleeding (may be severe) • Rash (may be severe)	• Injection site reactions • Hypersensitivity • Vision changes • Arrhythmia • Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Hemolysis • Pancreatitis • Pneumonitis • Rhabdomyolysis • SIADH

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G - Interactions

Refer to mesna, ifosfamide drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to mesna, ifosfamide drug monograph(s) for additional details

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and at each visit
- Urinalysis, for RBCs; before each dose
- Liver function tests; baseline and regular
- Renal function tests and electrolytes; baseline and regular
- Clinical assessment of neurotoxicity (especially in patients with increased risk) infection, bleeding, local toxicity and cystitis; at each visit

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

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J - Administrative Information

Approximate Patient Visit	Ifosfamide split into multiple days: 6-7 hours

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K - References

Ifosfamide and mesna drug monographs, Cancer Care Ontario.

Soft Tissue:

Bramwell VH, Mouridsen HT, Santoro A, et al. Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. Eur J Cancer Clin Oncol 1987;23(3):311-21.

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.

Osteogenic:

Daw NC, Billups CA, Rodriguez-Galindo C, et al. Metastatic osteosarcoma. Cancer 2006;106(2):403-12.

Harris MB, Gieser P, Goorin AM, et al. Treatment of metastatic osteosarcoma at diagnosis: a Pediatric Oncology Group Study. J Clin Oncol 1998;16(11):3641-8.

Magrath I, Sandlund J, Raynor A, et al. A phase II study of ifosfamide in the treatment of recurrent sarcomas in young people. Cancer Chemother Pharmacol 1986;18 Suppl 2:S25-8.

Marti C, Kroner T, Remagen W, et al. High-dose ifosfamide in advanced osteosarcoma. Cancer Treat Rep 1985;69(1):115-7.

November 2017 aligned disease site with CCO website, aligned mesna dosing with QBP

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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