Regimen Monograph

A - Regimen Name

ETOPIFOS Regimen

Etoposide-Ifosfamide (may be part of IE-VAC)

Disease Site
Sarcoma - Ewing's
Sarcoma - Soft Tissue

Intent
Neoadjuvant
Adjuvant
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.

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B - Drug Regimen

etoposide	100 mg /m²	IV	Days 1 to 5
ifosfamide	1800 mg /m²	IV	Days 1 to 5

mesna

Various dosing schedules have been used. The following is an example (from ASCO guideline, Hensley 2009):

Mesna	Route	Timing
20% of Ifosfamide dose	IV	15 minutes pre-Ifosfamide
40% of Ifosfamide dose	PO	4 hours and 8 hours post-ifosfamide

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C - Cycle Frequency

ETOPIFOS: Repeat every 3 weeks

IE-VAC: Used in an alternating schedule with VAC* for a total of 14 cycles given **every 3 weeks** (7 of each) in the absence of progression or unacceptable toxicity.

Intensified IE-VAC† (for Ewing's sarcoma): Used in an alternating schedule with VAC* for a total of 14 cycles (7 of each) given **every 2 weeks**. G-CSF Prophylaxis is recommended with this regimen

† Note that only patients less than 50 years old were included in the clinical trial by Womer et al.
* Refer to VAC regimen.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

- Standard regimens for ifosfamide hydration should be followed. Refer to local guidelines.

- Oral hydration is also strongly encouraged; poorly hydrated patients may need more IV hydration. Inadequate total hydration may result in dose-related hemorrhagic cystitis
- Also refer to CCO Antiemetic Summary
- Consider G-CSF prophylaxis for patients at high risk of febrile neutropenia

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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 have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Worst Toxicity / Counts (x10^9/L) in previous cycle		**Worst Toxicity / Counts (x 10^9/L) in previous cycle**	**Action**
ANC <1.5	OR	Platelet < 100	Hold *; consider G-CSF if repeated delay and reduce dose by 25% if delayed >7 days despite G-CSF
Febrile Neutropenia OR ANC < 0.5 for ≥ 5-7 days	OR	Thrombocytopenic bleeding OR Platelets < 25	Hold *, then 75% or consider GCSF if isolated neutropenia. If recurs despite GCSF, reduce dose by 25%
Cardiotoxicity**			Consider discontinuing ifosfamide when LVEF ≤ 45%
Grade 3 or 4 mucositis, diarrhea or typhlitis			Hold*; restart with 25% ↓ in dose with etoposide
Grade 1 or 2 somnolence or other signs of encephalopathy			Hold ifosfamide; methylene blue 50mg IV q4h until resolution. Consider prophylactic methylene blue for subsequent cycles. Consider discontinuing or dose reduce for ifosfamide for next cycle.

Worst Toxicity / Counts (x10^9/L) in previous cycle		Worst Toxicity / Counts (x 10^9/L) in previous cycle	Action
Grade 3 or 4 CNS toxicity			Manage appropriately. Discontinue ifosfamide
Grade 3 related other organ / non-hematologic			*75% for suspect drug(s)
Grade 4 related other organ / non-hematologic; Hypersensitivity			Discontinue

*Do not restart until platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L, and toxicities have recovered to ≤ grade 2 (and until resolution of neuro- or CNS toxicity).

**including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, a greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.

Management of Urotoxicity

Finding	Action
Microscopic hematuria	Hold ifosfamide until resolves. Consider increasing mesna dose (e.g. double) in subsequent cycle.
Macroscopic hematuria	Discontinue or reduce ifosfamide dose

Hepatic Impairment

Bilirubin		AST/ALT	Etoposide (% previous dose)	Ifosfamide* (% previous dose)
1-2 x ULN	and/ or	<2 x ULN	50%	100%
2-4 x ULN		2-5 x ULN	25%	75%
> 4 x ULN		> 5 x ULN	Discontinue	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

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

Dosage in the elderly:

- Exercise caution as the elderly population may have decreased hepatic, renal, cardiac or hematopoietic function. Increases in ifosfamide half-life has been observed with advancing age; however, no significant changes in clearance were reported.
- No dose adjustment required for etoposide

Children:

- Safety and efficacy have not been fully established. 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 - Adverse Effects

Refer to etoposide, 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
• Dysgeusia (oral mesna) • Alopecia • Nausea, vomiting • Myelosuppression +/- infection, bleeding (may be severe) • Abdominal pain • Hemorrhagic cystitis (may be severe) • Neurotoxicity (including encephalopathy-may be severe) • Anorexia • Diarrhea • Flu-like symptoms	• Hypersensitivity • Cardiotoxicity • Arrhythmia • Arterial thromboembolism • Venous thromboembolism • Hemolysis, hemolytic uremic syndrome • Pancreatitis • Pneumonitis • Rhabdomyolysis • SIADH • Secondary malignancies • Disseminated intravascular

• Nephrotoxicity (may be severe) • Injection site reactions	coagulation • Renal tubular acidosis • Radiation recall reaction • Rash

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G - Interactions

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

- Increased neurotoxicity has been reported with ifosfamide and aprepitant; caution and monitor closely if used together
- P-glycoprotein inhibitors can reduce clearance and increase etoposide toxicity
- Use drugs that inhibit phosphatase with caution (e.g. levimasole) due to increased etoposide toxicity
- CYP3A4 inhibitors can decrease metabolism and increase etoposide levels. Use with caution; may require dose adjustment
- Monitor PT/INR closely for patients who are on warfarin due to possible increased anticoagulant effects
- Glucosamine may decrease the efficacy of etoposide; avoid
- 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.
- Drugs acting on the CNS have additive CNS effects with ifosfamide. Discontinue if possible.
- Hepatic-enzyme inducing drugs may increase ifosfamide toxicity; use with caution and monitor
- Nephrotoxic, ototoxic and cardiotoxic drugs can increase the risk of ifosfamide toxicity; use with caution and monitor

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H - Drug Administration and Special Precautions

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

Administration

Etoposide:

- Maximum diluted concentration of 0.4 mg/mL

- All premixed bag(s) should be attached to (0.22 micron) in-line filter.
- Precipitation is unpredictable, depending on concentration, time after dilution, presence of crystallization nuclei, agitation, contact with incompatible surfaces and other factors.
- Monitor solutions for precipitation before and during administration.
- Dilute doses ≤100 mg in 250 mL NS or D5W, doses >100 mg to ≤200 mg in 500 mL, and doses> 200 mg in 1000 mL
- The use of non-PVC containers and tubing is recommended due to the potential for polysorbate 80 leaching of diethylhexyl phthalate (DEHP), from polyvinyl chloride (PVC) containers and tubing into etoposide IV solution.
- Larger volumes may be used for prehydration for Cisplatin or Ifosfamide dose.
- Infuse over 30 to 60 minutes; Adjust rate if blood pressure drops. Etoposide should not be given by rapid I.V. injection.
- May observe patient for 30 minutes after dose, to watch for hypotension.
- Acrylic or ABS (a polymer composed of acrylonitrile. butadiene and styrene) infusion devices may crack if exposed to undiluted etoposide.

Ifosfamide:

- 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 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.

Contraindications

- Etoposide is contraindicated in patients with known hypersensitivity to etoposide or to any component of the formulation (polysorbate 80), with severe myelosuppression, or with severe hepatic and/or renal impairment. Patients with low serum albumin may be at an increased risk of toxicity.
- 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.
- Avoid the use of live vaccines.

Other warnings/precautions

- Mesna must be coadministered with ifosfamide.
- 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.
- Electrolytes imbalances must be corrected before treatment.
- Alcohol can increase the risk of nausea/vomiting or neurotoxicity; avoid
- Etoposide and ifosfamide are not recommended for use in pregnancy or breastfeeding. Effective contraception must be used by both sexes during ifosfamide treatment and for at least 12 months after treatment cessation. Fertility is usually affected.

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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

- CBC; Baseline and prior to each dose
- Liver function tests; Baseline and prior to each dose
- Renal function tests, including electrolytes; Baseline and prior to each dose
- Urinalysis, for RBCs and specific gravity; before each ifosfamide dose
- Clinical assessment of hypertension, infection, bleeding and cystitis,neurotoxicity (especially in patients with increased risk), rash, GI symptoms (including stomatitis), infusion site reactions and hypersensitivity; 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	4.5 hours
Pharmacy Workload (average time per visit)	34.992 minutes
Nursing Workload (average time per visit)	54.167 minutes

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K - References

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February 2018 aligned mesna dosing with ST-QBP; modified intents

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M - Disclaimer

Regimen Abstracts

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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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