Regimen Monograph

A - Regimen Name

EP-EMA Regimen

PLATINOL® (CISplatin)-Etoposide-Methotrexate-Actinomycin (Dactinomycin)

Disease Site	Gynecologic - Gestational Trophoblastic Disease (GTD)
Intent	Curative
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.
Rationale and Uses	Treatment for patient with high risk (WHO≥7) GTD who has become refractory to EMA-CO chemotherapy (i.e. 2nd line therapy for the treatment of choriocarcinoma), and for the 1st line treatment of placental site trophoblastic tumours (PSTT).

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B - Drug Regimen

EP:

etoposide	150 mg /m²	IV	Day 1
CISplatin	75 mg /m²	IV *	Day 1

(*In a clinical trial, it was given as 25 mg/m^2 IV in 1000mL Nornal Saline over 4 hours for 3 doses)

EMA:

etoposide	100 mg /m²	IV	Day 8
methotrexate	300 mg /m²	IV over 12 hours	Day 8

Beginning 24 hours after the start of methotrexate, give leucovorin as follows:

leucovorin	15 mg	PO	Every 6 hours x 4 doses

Day 8:

DACTINomycin	0.5 mg	IV	Day 8

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

(EP and EMA are alternated at weekly intervals starting with EP)

Treatment continued for 2-4 courses after documentation of the first normal hCG level

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (D1)
Moderate (D8)

Febrile Neutropenia Risk: High

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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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 (x 10^9/L) in previous cycle		**Worst Toxicity / Counts (x 10^9/L) in previous cycle**	**CISplatin (% previous dose)**	**etoposide (% previous dose)**	**methotrexate (% previous dose)**	**dactinomycin (% previous dose)**
ANC <1.5	Or	Platelet < 100	Hold *			
Febrile Neutropenia Or ANC < 0.5 for ≥ 5-7 d	Or	Thrombocytopenic bleeding Or Platelets < 25	Hold *, then 75% (consider GCSF for isolated neutropenia)			
Grade 2 neurotoxicity /ototoxicity			↓ 25%	No change	No change	No change
Grade 3 or 4 neurotoxicity/ototoxicity			Discontinue	No change	Discontinue if CNS neurotoxicity	No change
Grade 3 related organ / non-hematologic			*75% for suspect drug(s). if isolated mucositis related to methotrexate may consider doubling the dose of leucovorin prior to dose reduction			
Suspected pneumonitis			Hold, investigate appropriately and discontinue if confirmed			
Grade 4 related organ /			Discontinue			

non-hematologic Hemolysis, optic neuritis, thromboembolism, severe hypersensitivity reactions, grade 3 or 4 ↑ LFTs Leucoencephalopathy, viral reactivation			

*Do not start new cycle until toxicities have recovered to ≤ grade 2, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.

Overdose or Severe Methotrexate Toxicity: Can be treated with prompt leucovorin rescue. Acute, intermittent dialysis with a high-flux dialyzer has also been used. Hydration and urinary alkalinization may prevent the precipitation of methotrexate and/or its metabolites in the renal tubules. There have been case reports of intravenous carboxypeptidase G2 use in cases of overdose to hydrolyze methotrexate to inactive metabolites and hasten clearance.

Hepatic Impairment

Bilirubin (µmol/L)	Etoposide (% usual dose)	Methotrexate (% usual dose)	Dactinomycin (% usual dose)	Cisplatin
1-2 x ULN	50	Caution*	Caution*	No change
>2 - 2.5 x ULN	25	Caution*	50-66%	
>2.5 - 4 x ULN	25	75*		
>4 x ULN	Discontinue	Discontinue		No change

*Consider reducing dose if LFTs >3 x ULN

Renal Impairment

Creatinine clearance (mL/min)	Cisplatin (% usual dose)	Etoposide % usual dose	Methotrexate (% usual dose)	Dactinomycin (% usual dose)
>80	No change	No change	100%	No adjustment required
>60-80	No change	No change	60-75%	
>50-60	75	No change	50-60%	
>30-50	50	75	Discontinue	
15-30	Discontinue	75		
<15		50, or discontinue		

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F - Adverse Effects

Refer to etoposide, CISplatin, methotrexate, leucovorin, DACTINomycin drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Nausea, vomiting • Alopecia • Nephrotoxicity • Neurotoxicity, ototoxicity (may be severe) • Diarrhea • Mucositis • Myelosuppression ± infection, bleeding (may be severe, includes opportunistic) • Anorexia • ↑ LFTs (may be severe) • Abnormal electrolytes • Rash (may be severe)	• Hypotension • Hypersensitivity • Arterial thromboembolism • Arrhythmia • GI perforation • Hemolytic uremic syndrome, hemolysis • Leukoencephalopathy • Optic nerve disorder • Pancreatitis • Pneumonitis • Secondary malignancy • Seizure • Vasculitis • Veno-occlusive disease • Venous thromboembolism

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G - Interactions

Refer to etoposide, CISplatin, methotrexate, leucovorin, DACTINomycin drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to etoposide, CISplatin, methotrexate, leucovorin, DACTINomycin drug monograph(s) for additional details

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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 before each cycle
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium.; baseline and regular
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Audiogram; as clinically indicated
- Clinical toxicity assessment of infection, bleeding, GI (stomatitis, nausea/vomiting, diarrhea), skin, pulmonary, or CNS or peripheral neurotoxicity, ototoxicity, infusion reactions; at each visit

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

Suggested Clinical Monitoring

- Lung function tests if pulmonary toxicity suspected
- Hepatitis B and Hepatitis C infection testing; Baseline

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J - Administrative Information

Approximate Patient Visit	Usually as inpatient
Pharmacy Workload (average time per visit)	43.501 minutes
Nursing Workload (average time per visit)	54.167 minutes

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K - References

Dobson LS, Lorigan PC, COleman RE, et al. Persistent gestational trophoblastic disease: results of MEA (methotrexate, etoposide and dactinomycin) as first-line chemotherapy in high risk disease and EA (etoposide and dactinomycin) as second-line therapy for low risk disease. Br J Cancer 2000;82(9):1547-52.

Newlands ES, Mulholland PJ, et al. Etoposide and cisplatin/etoposide, methotrexate, and Actinomycin D (EMA) for patients with high risk gestational trophoblastic tumors refractory to EMA/cyclophosmphamide and vincristine chemotherapy and patients presenting with metatstatic placental site trophoblastic tumours. J Clin Oncol 2000 Feb; 18(4) : 854-59.

Society of Gynecologists and Obstetricians of Canada Clinical Practice Guidelines: Gestational Trophoblastic Disease.

June 2020 Updated hyperlinks to dactinomycin drug monograph

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M - Disclaimer

Regimen Abstracts

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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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