Regimen Monograph

A - Regimen Name

MIDO Regimen

Midostaurin

Disease Site

Hematologic
Rare Diseases

(Mastocytosis)

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.

Rationale and Uses

For treatment of advanced systemic mastocytosis.

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B - Drug Regimen

midostaurin	100 mg	PO	BID

(This drug is not currently publicly funded for this regimen and intent)

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C - Cycle Frequency

CONTINUOUS TREATMENT

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate – Consider prophylaxis daily

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.

- Midostaurin should be stopped prior to the administration of any HSCT conditioning regimens.
- Use only in patients ≥ 60 years of age if they are eligible for intensive induction regimens and have adequate performance status and no significant comorbidities
- Active serious infections should be under control prior to starting treatment .

Dosage with toxicity

Dose Levels

Dose Level	Midostaurin Dose (mg BID)
0	100
-1	50

Hematological Toxicities**

Toxicity	Criteria	Action
Neutropenia	ANC < 1 x 10^9/L (in patients without MCL)	Hold until recovery to ≥ 1.5x 10^9/L. Resume at 1 dose level ↓. If tolerated, may ↑ 1 dose level. Discontinue if low ANC persists for > 21 days.
	ANC < 0.5 x 10^9/L (in patients with baseline ANC value of 0.5-1.5 x 10^9/L)	
Thrombocytopenia	Platelets < 50 x 10^9/L (in patients without MCL)	Hold until recovery to ≥ 50x 10^9/L. Resume at 1 dose level ↓. If tolerated, may ↑ 1 dose level. Discontinue if low platelet count persists for > 21 days.
	Platelets < 25 x 10^9/L (in patients with baseline platelet count of 25-75 x 10^9/L)	
Hemoglobin	<80 g/L (in patients without MCL)	Hold until recovery to ≥ 80 g/L. Resume at 1 dose level ↓. If tolerated, may ↑ 1 dose level. Discontinue if low hemoglobin persists for > 21 days.
	Life-threatening anemia in patients with baseline hemoglobin of 80 -100 g/L	

**Attributed to midostaurin

Nonhematologic Toxicities:

Toxicity	Grade	Action
Nausea/vomiting	≥ Grade 3^	Hold for 3 days (6 doses). Resume at 1 dose level ↓. If tolerated, may ↑ 1 dose level.
Other non-hematological toxicities	≥ Grade 3	Hold until recovery to ≤ grade 2. Resume at 1 dose level ↓. If tolerated, may ↑ 1 dose level.

^Despite optimal antiemetic prophylaxis

Hepatic Impairment

Hepatic Impairment	Midostaurin Dose
Mild or Moderate (Child-Pugh A or B)	No dose adjustment needed
Severe (Child-Pugh C)	Caution (no data available)

Renal Impairment

Renal Impairment	Midostaurin Dose
Mild or Moderate (CrCl ≥ 30 mL/min)	No dose adjustment needed
Severe (CrCl 15-29 mL/min)	Caution; data is limited.
End-stage renal disease	No data

Dosage in the Elderly

- No dose adjustment required.
- Clinical studies in SM and MCL demonstrated no overall differences in safety or response rate in patients ≥65 years of age compared to younger patients. Use with caution.

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F - Adverse Effects

Refer to midostaurin drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection, bleeding (may be severe) • Nausea, vomiting (generally mild) • Dermatitis exfoliative (may be severe) • Diarrhea	• Headache • Peripheral edema • Fatigue • Constipation	• Mucositis • Musculoskeletal pain • QT interval prolonged • Hyperglycemia (may be severe) • Abdominal pain • Cough, dyspnea • Hypersensitivity • Hemorrhoids • Hyperhidrosis • INR / prothrombin time increased (activated partial thromboplastin time) • Insomnia • Pharyngolaryngeal pain • Arrhythmia	• Cardiac failure • Pericardial effusion • Thromboembolism (catheter-related) • ↑ LFTs • Hyperuricemia • Pneumonitis • Pleural effusion • Acute respiratory distress syndrome • Interstitial lung disease

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G - Interactions

Refer to midostaurin drug monograph(s) for additional details

- Avoid concomitant use with strong CYP3A4 inhibitors as co-administration may lead to increased midostaurin exposure. If strong inhibitors must be used concomitantly, closely monitor for toxicity, especially during the first week of each cycle.

- Avoid concomitant use with strong CYP3A4 inducers as co-administration may lead to decreased midostaurin exposure.
- Monitor closely when co-administered with drugs that prolong QT interval due to additive effects and increased risk of torsades de pointes.

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H - Drug Administration and Special Precautions

Refer to midostaurin drug monograph(s) for additional details

Administration

- Midostaurin should be taken orally, twice daily, approximately 12 hours apart.
- Administer with food to help prevent nausea. Prophylactic antiemetics may be necessary.
- Capsules should be swallowed whole with a glass of water and not opened, crushed, or chewed.
- If a dose is missed, it should be skipped and the next scheduled dose taken at the scheduled time.
- If vomiting occurs, no additional dose should be taken and the next scheduled dose should be taken at the scheduled time.
- Grapefruit, starfruit, Seville oranges, their juices or products during treatment should be avoided.
- Store in the original package at room temperature (not above 30ºC).
- Keep out of reach and sight of children and pets.

Contraindications

- In patients with hypersensitivity to midostaurin or to any components of the formulation.

Other Warnings/Precautions

- Patients with serum creatinine > 20mg/L, LFTs > 2.5 x ULN or > 5 x ULN if disease-related and total bilirubin > 1.5 x ULN or > 3 x ULN if disease-related were excluded from clinical trials.

- Caution in patients with increased risk for torsade de pointes and with concomitant QTc interval-prolonging drugs. SM and MCL trials excluded patients with a baseline QTcF> 450ms.
- Caution in patients at risk for heart failure. Patients with symptomatic congestive heart failure were excluded from clinical studies.

Pregnancy / Lactation

- Midostaurin is not recommended for use in pregnancy. If pregnancy is possible, adequate contraception should be used by both sexes during treatment and for at least **4 months** after the last dose. It is unknown if midostaurin reduces the effectiveness of hormonal contraceptives; a barrier method should also be used.
- Breastfeeding is not recommended during treatment and for at least **4 months** after stopping treatment.
- Fertility Effects: Probable
    - Midostaurin was associated with reproductive toxicity in both males and females in animal studies.

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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, before each cycle and as clinically indicated; more frequently at treatment initiation
- Liver function tests; Baseline, before each cycle and as clinically indicated
- Renal function tests; Baseline, before each cycle and as clinically indicated
- LVEF; Baseline and as clinically indicated, especially if risk factors
- ECG; Baseline and as clinically indicated if patient is concurrently taking drugs that

can prolong QT interval

- Blood glucose; Baseline, at each visit and as clinically indicated
- Clinical toxicity assessment for signs and symptoms of infection, heart failure, dermatological, hypersensitivity, GI, hyperuricemia, and pulmonary symptoms; Baseline and at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

INR, aPTT; Baseline and at each visit

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med.. 2016;374(26):2530-2541.

Midostaurin Drug Monograph, Ontario Health (Cancer Care Ontario.)

April 2022 Expanded to full Regimen Monograph

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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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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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