Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

midostaurin

COMMON TRADE NAME(S): Rydapt®

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B - Mechanism of Action and Pharmacokinetics

Midostaurin is a tyrosine kinase inhibitor that targets multiple receptors (including FLT3, KIT kinase). It inhibits FLT3 receptor signaling in leukemic cells that express internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutant receptors or overexpressing wild type receptors, inducing cell cycle arrest and apoptosis. Midostaurin inhibits the wild type and D816V mutant KIT, interfering with KIT signaling and inhibits cell proliferation and survival, and histamine release in mast cells. It also binds to the catalytic domain of multiple kinases (PDGF-R, VEGFR2, etc.) to inhibit cell growth.

Absorption	Time to reach steady state	28 days
	Effects with food	AUC ↑ by 22% with standard meal and 59% with high-fat meal. Cmax ↓ by 20% with standard meal and 27% with high fat meal. Time to peak concentration was increased with food as compared to fasting. In trials, midostaurin was administered with a meal to reduce toxicity.
	Peak plasma levels	1-3 hours (fasted state) 2.5-3 hours (with standard or high-fat meal)
Distribution	PPB	> 98% (mainly alpha-1-acid glycoprotein)

	Cross blood brain barrier?	Yes- animal studies
Metabolism	Midostaurin undergoes extensive hepatic metabolism through CYP3A4 enzymes.	
	Active metabolites	CGP62221 and CGP52421 (28% and 38% of total plasma exposure)
Elimination	Half-life	Median terminal $T_{1/2}$ of midostaurin, CGP62221 and CGP52421 = 21, 32, and 471 hours respectively
	Feces	78%; 73% as metabolites
	Urine	4%

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C - Indications and Status

Health Canada Approvals:

- Acute myeloid leukemia (AML)
- Systemic mastocytosis (SM)
- Mast cell leukemia (MCL)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Moderate – Consider prophylaxis daily

The following table lists adverse effects that occurred in the phase III study in patients with newly diagnosed FLT3-mutated AML in the midostaurin + chemotherapy arm. Only adverse effects that occurred at a frequency of >2% compared to the placebo + chemotherapy arm are listed. It also includes severe, life-threatening and post-marketing adverse effects from other sources. Adverse effects marked with "^" were observed in SM and MCL monotherapy, open-label studies.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (10%) (sinus tachycardia; 1% severe)	E
	Cardiotoxicity (rare)	E
	Hypertension (8%) (may be severe)	E
	Hypotension (6%) (severe)	E
	Pericardial effusion (4%)	E
	QT interval prolonged (20%) (6% severe)	E
	Thromboembolism (4%) (catheter-related)	E
Dermatological	Exfoliative Dermatitis (62%) (14% severe)	E
	Hyperhidrosis (14%)	E
Gastrointestinal	Abdominal pain (17%)	E
	Constipation (29%) ^	E
	Diarrhea (51%) ^	E
	Dyspepsia (6%) ^	E
	Hemorrhoids (15%)	E
	Mucositis (22%)	E
	Nausea, vomiting (83%) (6% severe)	E
General	Edema - limbs (35%) ^	E
	Fatigue (31%) ^	E
Hematological	INR / prothrombin time increased (13%) (activated partial thromboplastin time)	E
	Myelosuppression ± infection, bleeding (84%) (may be severe)	E
Hepatobiliary	↑ LFTs (9%) (ALT, AST) (severe)	E
Hypersensitivity	Hypersensitivity (16%) (<1% severe)	I E
Metabolic / Endocrine	Hyperglycemia (20%) (may be severe)	E
	Hyperuricemia (8%)	E

Musculoskeletal	Musculoskeletal pain (22%)	E
Nervous System	Confusion (6%) ^	E
	Headache (46%)	E
	Insomnia (12%)	E
	Syncope (5%)	E
	Tremor (4%)	E
Ophthalmic	Eye disorders (7%) (keratitis, eyelid edema)	E
Respiratory	Acute respiratory distress syndrome (ARDS) (2%)	E
	Cough, dyspnea (16%) ^	E
	Interstitial lung disease (rare)	E
	Pharyngolaryngeal pain (12%)	E
	Pleural effusion (6%)	E
	Pneumonitis (11%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for midostaurin include myelosuppression ± infection, bleeding, nausea, vomiting, diarrhea, headache, edema - limbs, fatigue, constipation, mucositis, musculoskeletal pain and hyperglycemia.

QT prolongation occurred at an increased frequency in patients on midostaurin. Caution in patients with suspected increased risk of torsade de pointes and if midostaurin is taken concomitantly with QTc interval-prolonging drugs.

Cardiac failure, including fatal cases and decreases in LVEF have been reported in trials of midostaurin 100mg bid.

Neutropenia and **infection**, including fatal cases, have been reported, including device-related infections. In the SM and MCL studies severe neutropenia (ANC less than 0.5 x 109/L) was generally reversible when midostaurin was withheld.

Pulmonary toxicity, including interstitial lung (ILD) disease and pneumonitis (fatal in some cases) have been reported.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Patients must have confirmation of FLT3 mutation with a validated test prior to starting AML induction treatment.

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 with midostaurin monotherapy.

Adults:

AML - Induction and Consolidation:

Oral: 50 mg BID on Days 8 to 21 of each chemotherapy cycle

Note:

- Midostaurin is given as part of induction with cytarabine and daunorubicin for up to 2 cycles of at least 24 days each if remission is not observed at the end of the first induction cycle.
- If complete remission, midostaurin is given with cytarabine consolidation therapy for up to 4 cycles (q 28 days minimum).

See CYTA(HD)+MIDO for the consolidation regimen details.

SM and MCL:

Oral: 100 mg BID

Dosage with Toxicity:

AML:

Toxicity	Grade	Action
Pulmonary infiltrates	≥ Grade 3	Hold for remainder of cycle. With recovery to ≤ grade 1, resume at same dose level.
Other non-hematological	≥ Grade 3	Hold until recovery to ≤ grade 2*, then resume at same dose level.

* toxicities considered at least possibly related to midostaurin

SM and MCL:

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

Dosage with 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)

Dosage with 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.
- There is limited experience in patients 60-70 years of age and no experience in patients >70 years of age in AML studies. In an interim analysis, serious adverse effects and deaths were slightly higher in patients ≥65 years of age compared to younger patients.

Dosage based on gender:

No dose adjustment required. In population PK analysis, gender did not have clinically meaningful effects on clearance.

Dosage based on ethnicity:

No dose adjustment based on ethnicity required. No differences in PK profile was shown between Caucasian and Black patients. In healthy Japanese volunteers, PK profiles of midostaurin and metabolites are similar compared to PK studies in Caucasians and Black patients.

Children:

There are limited data in pediatric patients and the safety and efficacy of midostaurin has not been established. Cases of markedly delayed hematological recoveries were reported in pediatric patients after the second induction chemotherapy cycle with midostaurin.

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F - Administration Guidelines

- 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.

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G - Special Precautions

Contraindications:

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

Other Warnings/Precautions:

- Patients with total bilirubin ≥ 2.5 × ULN were excluded from AML trials.
- SM and MCL trials excluded patients with serum creatinine > 20 mg/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.
- 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 and Lactation:

- Genotoxicity: No
- Mutagenicity: No
- Clastogenicity: No
- Fetotoxicity: Documented in animals
- Pregnancy:
  Midostaurin is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **4 months** after the last dose.
- Excretion into breast milk: Documented in animals
  Breastfeeding is not recommended during treatment and for at least **4 months** after the last dose.
- Fertility effects: Probable
  Documented in animal studies

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H - Interactions

In vitro data shows that midostuarin may increase the exposure of drugs cleared by CYP2D6, CYP2E1, P-gp, BCRP or OATP 1B1 and decrease the exposure of co-administered drugs primarily cleared by CYP2B6 and CYP2C19.

The effect on drugs that are substrates of CYP1A2, CYP2C8 or CYP2C9 is uncertain.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ exposure to midostaurin and metabolite CGP62221 (ketoconazole increased midostaurin Cmax and AUC by 1.8- and 10.4-fold, respectively)	↓ midostaurin metabolism	Avoid strong inhibitors. If strong inhibitors must be used concomitantly, closely monitor for toxicity, especially during the 1st week of each cycle.
Strong CYP3A4 inducers (i.e. rifampin, carbamazepine, St. John's Wort, etc)	↓ exposure to midostaurin and both active metabolites (rifampicin decreased midostaurin Cmax and AUC by 73% and 96% respectively)	↑ midostaurin metabolism	Avoid
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, etc.)	↑ risk of torsade de pointes	Additive	Caution; monitor closely
CYP3A4/5 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines)	unknown		Caution with drugs with narrow therapeutic index
CYP2D6, CYP2E1, P-gp, BCRP, BSEP or OATP1B1 substrates	↑ substrate exposure	↓ substrate metabolism	Caution with drugs with narrow therapeutic index

CYP2B6 and CYP2C19 substrates	↓ substrate exposure	↑ substrate metabolism	Caution with drugs with narrow therapeutic index
CYP1A2, CYP2C8 or CYP2C9 substrates	unknown	↑/↓ substrate metabolism	Caution with drugs with narrow therapeutic index
Drugs that disrupt electrolyte levels (e.g. loop, thiazide, and related diuretics; laxatives and enemas; proton pump inhibitors; amphotericin B, high-dose corticosteroids)		Additive	Caution

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
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

Monitor Type	Monitor Frequency
INR, aPTT	Baseline and at each visit

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- midostaurin - First-line treatment of adult patients diagnosed with FLT3-mutated acute myeloid leukemia, in combination with specific standard induction followed by consolidation chemotherapy, according to clinical criteria

High Cost Therapy Funding Program

- Midostaurin (Inpatient) - FLT3-mutated Acute Myeloid Leukemia

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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. doi:10.1056/NEJMoa1513098

Midostaurin (Rydapt®) Product Monograph. Novartis Pharmaceuticals Canada Inc. June 29, 2021 and March 31, 2023.

Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017; 377:454-464.

June 2025 Updated Pregnancy/Lactation section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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