DRUG NAME: Midostaurin

SYNONYM(S): PKC412, CGP 41251, N-benzoyl staurosporine[1]

COMMON TRADE NAME(S): RYDAPT®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Midostaurin is a multi-targeted, oral tyrosine kinase inhibitor which inhibits FMS-like tyrosine kinase 3 (FLT3) receptor signalling. Blocking FLT3 signalling induces apoptosis in cells which express mutant FLT3 or overexpress either wild type FLT3 or platelet-derived growth factor receptors (PDGFR). Midostaurin also inhibits KIT signalling, resulting in inhibition of histamine release and mast cell apoptosis.[2,3]

PHARMACOKINETICS:

Oral Absorption	time to peak: 1-3 h; time-dependent accumulation over first week, then non-linear decrease to steady state after ~28 days	
Distribution	distributed mainly in plasma	
	cross blood brain barrier?	yes (demonstrated in animals)
	volume of distribution	95 L
	plasma protein binding	98%
Metabolism	primarily by CYP 3A4	
	active metabolite(s)	CGP62221 (similar potency to parent drug); CGP52421 (10 times less potent than parent drug)
	inactive metabolite(s)	no information found
Excretion	mainly fecal elimination	
	urine	4%
	feces	78% (73% as metabolites, 3% parent drug)
	terminal half life	midostaurin (21 h); CGP62221 (32 h); CGP52421 (471 h)
	clearance	3.7 L/h[4]
Children	decreased exposure with increasing weight and age	

Adapted from standard reference[5] unless specified otherwise.

USES:

Primary uses:

*Leukemia, acute myeloid

*Mastocytosis, systemic

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:
- ***cardiac failure*** and ***decreased left ventricular ejection fraction*** have been reported; increased monitoring is suggested for patients with a cardiac history or at risk for cardiac failure[5]
- ***QT interval prolongation*** has been reported; monitor ECG and electrolytes in patients with known history of QT prolongation, risk factors for torsades de pointes, or taking concurrent medications known to prolong the QT interval[5]
- numerous potential ***drug interactions*** are listed, particularly with inducers or inhibitors of ***cytochrome P450 enzymes*** or ***P-glycoprotein***; dose adjustments may be required if interacting drugs must be taken concurrently[5]

Special populations:
- patients ***older than 60 years*** may experience a slightly higher frequency of severe adverse events than younger patients[5]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test or mammalian *in vitro* mutation tests. Midostaurin is clastogenic in mammalian *in vitro* chromosome tests but not in mammalian *in vivo* chromosome tests.[6]

Fertility: In animal studies, reduced pregnancy rates were reported in females, while testicular degeneration/atrophy, inhibition of spermatogenesis, decreased sperm count, and altered sperm motility were observed in males. It is not known whether these effects are reversible.[5]

Pregnancy: In animal studies, embryo-fetal toxicity (e.g., increased resorptions, reduced fetal weight, and delayed skeletal ossification) was reported. For females of reproductive potential, pregnancy testing is recommended within seven days prior to initiating treatment. Contraception should be used during treatment and for at least four months after the last dose of midostaurin. The efficacy of hormonal contraceptives may be reduced due to a possible interaction between midostaurin and these medications; therefore, females using hormonal contraceptives are advised to discuss contraceptive options with their physician.[5]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women may begin breastfeeding four months after the last dose of midostaurin.[3]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[7,8]. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[9] **Incidence data in the Side Effects table is based on midostaurin monotherapy data where possible; in some cases, incidence data based on combination therapy with cytarabine and daunorubicin[2,5] or azacitidine[10] has been included and is indicated with an asterisk (*).**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (60-63%, severe 38-41%)[5,6]
	febrile neutropenia (8-24%, severe 8-24%)[5,11]
	leucopenia (8-61%, severe 8-19%)[5,6]
	lymphopenia (17-66%, severe 42%)[5,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neutropenia (48-49%, severe 21-24%)[5,6,12]
	petechiae* (36%, severe 1%)
	thrombocytopenia (50-52%, severe 27-29%)[6,12]
cardiac	***cardiac failure*** (1-6%, severe 1-6%)[6,11]; has been fatal
	ejection fraction reduction* (15%, severe 11%)[10]
	myocardial infarction, ischemia (4%)[6]
ear and labyrinth	vertigo (5%)
gastrointestinal	*emetogenic potential:* moderate[13]
	abdominal pain (28-34%, severe 3-6%)[6,12]
	constipation (19-29%, severe ≤2%)[5,11]
	diarrhea (43-54%, severe 5-8%)[11,12]
	dyspepsia (6%)
	gastritis (3%)[6]
	gastrointestinal hemorrhage (4%, severe 4%)
	nausea (46-82%, severe 1-6%)[5,11,12]
	stomatitis*** (22%, severe 4%)
	vomiting (19-68%, severe 1-6%)[5,11]
general disorders and administration site conditions	chills (5%)
	edema (4%, severe <1%)
	edema, eyelid* (3%)
	edema, peripheral (22-35%, severe 2-4%)[5,11]
	fatigue (28-37%, severe 2-9%)[11,12]
	pyrexia (27-33%, severe 4-7%)[5,11,12]
immune system disorders	***hypersensitivity*** (2-4%)[2,5]
infections and infestations	bronchitis (6%)
	device-related infection*** (24%, severe 16%)
	erysipelas (4%)
	Herpesvirus infection (10%, severe 1%)[6]
	pneumonia (9-24%, severe 7-10%)[5,11]; has been fatal
	sepsis (8%, severe 8%)[5]; has been fatal
	skin infection (5%)[6]
	upper respiratory tract infection (30%, severe 1%)[6]
	urinary tract infection (12-16%, severe 2-3%)[6,12]
injury, poisoning, and procedural complications	bruising (6%)
	fall (4%, severe <1%)
investigations	amylase increase (20%, severe 7%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	alkaline phosphatase increase (39%, severe 9%)[6]
	ALT increase (9-31%, severe 4-9%)[5,6]
	AST increase (3-32%, severe 3%)[5,6]
	bilirubin increase (29%, severe 4%)[6]
	creatinine increase (25%, severe <1%)[6]
	gamma-glutamyltransferase increase (35%, severe 9%)[6]
	lipase increase (37%, severe 18%)[6]
	QT interval prolongation (10-11%, severe ≤1%)[12]
	weight increase (6%)
metabolism and nutrition	hyperglycemia (20-80%, severe 18%)[5,6]
	hyperkalemia (23%, severe 4%)[6]
	hypernatremia* (20%, severe 1%)
	hyperuricemia (37%, severe 11%)[6]
	hypoalbuminemia (27%, severe 1%)[6]
	hypocalcemia (39%, severe 2%)[6]
	hypokalemia (25%, severe 4-6%)[6,11]
	hypomagnesemia (20%)[6]
	hyponatremia (34%, severe 5%)[6]
	hypophosphatemia (22%, severe 1%)[6]
musculoskeletal and connective tissue	asthenia (5-19%, severe ≤2%)[5,11]
	arthralgia (17-19%, severe 2%)[6,12]
	back pain (20%, severe 2%)[12]
	musculoskeletal pain (16%, severe 4%)[12]
nervous system	cognitive disturbance (4%)[6]
	concentration impairment (7%)
	dizziness (11-13%)[5,12]
	headache (23-26%, severe 1-2%)[5,12]
	tremor (6%)
psychiatric	insomnia (11%)[6]
renal and urinary	***renal insufficiency*** (11%, severe 5%)[6]
respiratory, thoracic and mediastinal	cough (16-19%, severe ≤2%)[5,11,12]
	dyspnea (16-28%, severe 4-7%)[11,12]
	epistaxis (11-12%, severe 3-4%)[5,12]
	interstitial lung disease/pneumonitis (2%, severe ≤2%)[6]; see paragraph following **Side Effects** table
	oropharyngeal pain (4%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pleural effusion (11-13%, severe 3-4%)[5,12]
	pulmonary edema (3%)[6]
skin and subcutaneous tissue	***exfoliative dermatitis**** (62%, severe 14%)
	hyperhidrosis* (14%)
	pruritus (19%, severe 3%)[12]
	rash (14%, severe 3%)[6]
vascular	hematoma (6%, severe <1%)
	hypotension (9%, severe 2%)

Adapted from standard reference[5] unless specified otherwise.

Cases of ***interstitial lung disease*** and ***pneumonitis*** have been reported and are sometimes fatal.[5] Events have occurred during both midostaurin monotherapy and when combined with other chemotherapy.[3] For grade 3/4 pulmonary infiltrates/pneumonitis, midostaurin should be held for the remainder of the cycle. Midostaurin may be resumed at the same dose when toxicities have resolved to grade 1 or less.[5]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
grapefruit juice[5]	may increase plasma level of midostaurin	may inhibit CYP 3A4 metabolism of midostaurin in the intestinal wall	avoid grapefruit and grapefruit juice for the duration of treatment
ketoconazole[5]	midostaurin C_{max} and AUC increased 1.8-fold and 10.4-fold, respectively; AUC of CGP62221 metabolite increased 3.5-fold	strong inhibition of CYP 3A4 by ketoconazole	avoid concurrent use
itraconazole[3,5]	midostaurin C_{min} increased 2.1-fold	strong inhibition of CYP 3A4 by itraconazole	avoid concurrent use
rifampin[5]	midostaurin C_{max} and AUC decreased by 73% and 96%, respectively; both active metabolites exhibit a similar pattern	strong induction of CYP 3A4 by rifampin	avoid concurrent use

Midostaurin is a substrate of CYP 3A4. ***CYP 3A4 inhibitors*** may increase exposure to midostaurin; avoid concurrent use of ***strong CYP 3A4 inhibitors***. If there is no therapeutic alternative for the CYP 3A4 inhibitor, monitor closely for midostaurin toxicity. Midostaurin exposure may be decreased with concurrent use of ***CYP 3A4 inducers***; avoid concurrent use of ***strong CYP 3A4 inducers***.[5]

Midostaurin and its active metabolites can both induce and inhibit ***CYP 3A4/5, CYP 1A2, CYP 2C8,*** and ***CYP 2C9*** *in vitro*; clinical significance is unknown.[5]

In vitro, midostaurin and its active metabolites inhibit ***CYP 2D6, CYP 2E1, P-gp, BCRP,*** and ***OATP1B1***, potentially increasing exposure of coadministered ***substrates*** of these enzymes. Conversely, midostaurin induces ***CYP 2B6*** and ***CYP 2C19*** *in vitro*, potentially decreasing exposure of coadministered ***substrates*** of these enzymes. Clinical significance is unknown.[5]

Midostaurin is associated with ***QTc prolongation***. Avoid concurrent therapy with drugs associated with QTc prolongation, torsades de pointes, and/or drugs that disrupt electrolyte levels, if possible. If unavoidable, monitor for QT prolongation or cardiac arrhythmias.[5]

SUPPLY AND STORAGE:

Oral: Novartis Pharmaceuticals supplies midostaurin as 25 mg liquid-filled gelatin capsules. Keep in original blister packaging to protect from moisture. Store at room temperature. Capsules contain benzyl alcohol and ethanol.[5]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:	Cycle Length: 24-28 days minimum[5,9,14]:	induction and consolidation: ***50 mg PO twice a day*** for ***14 consecutive days*** starting on day 8
	28 days[9]:	maintenance: 50 mg PO twice daily continuously Patients proceeding to stem cell transplant (SCT) should stop midostaurin before the SCT conditioning regimen.
	100 mg PO twice a day, continuously[5,12]	
	Administering with food may help reduce nausea.[5] Swallow capsules whole; puncturing, crushing, or chewing capsules may lead to loss of active ingredient.[15]	
Concurrent radiation:	no information found	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	creatinine clearance ≥30 mL/min: no adjustment required[5] creatinine clearance <30 mL/min: no information found	
	calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$ * For males N=1.23; for females N=1.04	
Dosage in hepatic failure:	mild or moderate impairment (Child-Pugh A or B): no adjustment required[5] severe impairment (Child-Pugh C): no information found	
Dosage in dialysis:	significant drug removal is considered unlikely during dialysis due to the pharmacokinetic properties of midostaurin[16]	

Children: safety and efficacy has not been established[5]

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