Midostaurin (mye doe STAW rin)

Related Information
- Common Toxicity Criteria on page 2242
- Safe Handling of Hazardous Drugs on page 2379

Brand Names: US Rydapt
Brand Names: Canada Rydapt

Index Terms CGP 41251; N-benzoyl-staurosporine; PKC 412

Pharmacologic Category Antineoplastic Agent, FLT3 Inhibitor; Antineoplastic Agent, Tyrosine Kinase Inhibitor

Use
Acute myeloid leukemia, FLT3-positive: Treatment of adult patients with newly diagnosed FLT3 mutation-positive (as detected by an approved test) acute myeloid leukemia (AML), in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy

Limitations of use: Not indicated as single-agent induction therapy for the treatment of patients with AML.

Mast cell leukemia: Treatment of adult patients with mast cell leukemia (MCL)

Systemic mastocytosis: Treatment of adult patients with aggressive systemic mastocytosis (ASM) or systemic mastocytosis with associated hematological neoplasm (SM-AHN)

Labeled Contraindications Hypersensitivity to midostaurin or any component of the formulation

Pregnancy Considerations Adverse events were observed in animal reproduction studies with doses providing less than the human exposure at the recommended dose based on AUC. Based on the mechanism of action, midostaurin may cause fetal harm if used in pregnant women.

Pregnancy status should be verified within 7 days prior to therapy initiation. Females of reproductive potential and males with female partners of reproductive potential should use effective contraception during therapy and for at least 4 months after the last dose. Based on animal data, treatment with midostaurin may impair fertility in males and females.

Breastfeeding Considerations It is not known if midostaurin is present in breast milk. Due to the potential for adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for at least 4 months after the last dose.

Warnings/Precautions Lymphopenia, leukopenia, neutropenia, thrombocytopenia and anemia have been commonly observed in patients with systemic mastocytosis. Although the incidence of hematologic toxicity in acute myeloid leukemia (AML) may be confounded by concomitant chemotherapy, febrile neutropenia was reported at a slightly higher incidence in patients with AML receiving chemotherapy plus midostaurin (compared to chemotherapy plus placebo). Monitor blood counts. Nausea and vomiting commonly occur; premedicate with antiemetics prior to administration. Diarrhea, abdominal pain, and constipation also occur frequently. Mucositis has also been reported.

Hypersensitivity reactions, including anaphylactic shock, angioedema, dyspnea, chest pain and flushing have been observed. Interstitial lung disease and pneumonitis have been reported with midostaurin (either as monotherapy or in combination with other chemotherapy), some cases have been fatal. Monitor for pulmonary symptoms; discontinue in patients who develop signs/symptoms of interstitial lung disease or pneumonitis (without an infectious etiology).
Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy.

**Adverse Reactions**

>10%:
- Cardiovascular: Edema (40%), prolonged Q-T interval on ECG (11%)
- Central nervous system: Headache (26% to 46%), fatigue (34%), dizziness (13%), insomnia (11% to 12%)
- Dermatologic: Hyperhidrosis (14%), skin rash (14%)
- Endocrine & metabolic: Hyperglycemia (20% to 80%), hypocalcemia (39% to 74%), hyperuricemia (8% to 37%), increased gamma-glutamyl transferase (35%), hyponatremia (34%), hypoalbuminemia (27%), hypokalemia (25%), hyperkalemia (23%), hypophosphatemia (22%), hypernatremia (21%), hypomagnesemia (20%)
- Gastrointestinal: Nausea (47% to 83%), vomiting (19% to 68%), mucositis (66%), diarrhea (54%), increased serum lipase (37%), abdominal pain (34%), constipation (29%), increased serum amylase (20%), hemorrhoids (15%), gastrointestinal hemorrhage (14%)
- Genitourinary: Urinary tract infection (16%)
- Hematologic & oncologic: Febrile neutropenia (8% to 83%; grades ≥3: 84%), lymphocytopenia (66%; grades ≥3: 42%), leukopenia (61%; grades ≥3: 19%), anemia (60%; grades ≥3: 38%), thrombocytopenia (50%; grades ≥3: 27%), neutropenia (49%; grades ≥3: 22%), petechia (36%), prolonged partial thromboplastin time (13%; grades ≥3: 3%)
- Hepatic: Increased serum ALT (31% to 71%), increased serum alkaline phosphatase (39%), increased serum AST (32%), hyperbilirubinemia (29%)
- Infection: Localized infection (24%; device related)
- Neuromuscular & skeletal: Musculoskeletal pain (33% to 35%), arthralgia (14% to 19%)
- Renal: Increased serum creatinine (25%), renal insufficiency (11% to 12%)
- Respiratory: Upper respiratory tract infection (20% to 30%), epistaxis (12% to 28%), dyspnea (23%), cough (18%), pleural effusion (6% to 13%)
- Miscellaneous: Fever (27%)

1% to 10%:
- Cardiovascular: Hypotension (9%), hypertension (8%), cardiac failure (6%), thrombosis (5%), pericardial effusion (4%), ischemia (≤4%), myocardial infarction (≤4%)
- Central nervous system: Disturbance in attention (7%), chills (5%), vertigo (5%), mental status changes (4%)
- Dermatologic: Xeroderma (7%), cellulitis (≤7%), erysipelas (≤5%)
- Endocrine & metabolic: Weight gain (6% to 7%), hypercalcemia (3%)
- Gastrointestinal: Dyspepsia (6%), gastritis (3%)
- Hematologic & oncologic: Bruise (6%), hematoma (6%)
- Hypersensitivity: Hypersensitivity (4%)
- Infection: Herpes virus infection (10%), sepsis (9%), fungal infection (7%)
- Neuromuscular & skeletal: Tremor (4% to 6%)
- Ophthalmic: Eyelid edema (3%)
- Respiratory: Pneumonia (10%), bronchitis (6%), oropharyngeal pain (4%), pulmonary edema (3%), interstitial pulmonary disease (≤2%), pneumonia (≤2%)
Drug Interactions

**Metabolism/Transport Effects Substrate of CYP3A4 (major); Note:**
Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** SLCO1A1; **Induces** MRP2

**Avoid Concomitant Use**
Avoid concomitant use of Midostaurin with any of the following: BCG (Intravesical); CYP3A4 Inducers (Strong); Deferiprone; Dipyrone; Fusidic Acid (Systemic); Highest Risk QTc-Prolonging Agents; Hydroxychloroquine; Idelalisib; MiFEPRIStone; Probucol; Promazine; St John's Wort; Vinflunine

**Increased Effect/Toxicity**
Midostaurin may increase the levels/effects of: Deferiprone; Highest Risk QTc-Prolonging Agents; Moderate Risk QTc-Prolonging Agents

The levels/effects of Midostaurin may be increased by: Aprepitant; Convivapan; CYP3A4 Inhibitors (Moderate); CYP3A4 Inhibitors (Strong); Dasatinib; DiRTIAZem; Dipyrone; Fosaprepitant; Fusidic Acid (Systemic); Grapefruit Juice; Hydroxychloroquine; Idelalisib; MiFEPRIStone; Netupitant; Palbociclib; Probucol; Promazine; QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying); Simeprevir; Striplentol; Vinflunine; Xipamide

**Decreased Effect**
Midostaurin may decrease the levels/effects of: Antidiabetic Agents; BCG (Intravesical)

The levels/effects of Midostaurin may be decreased by: Bosentan; CYP3A4 Inducers (Moderate); CYP3A4 Inducers (Strong); Dabrafenib; Deferasirox; Sarilumab; Siltuximab; St John's Wort; Tocilizumab

**Food Interactions**
Grapefruit juice may increase midostaurin plasma concentration. Management: Avoid grapefruit juice.

**Hazardous Drugs Handling Considerations**
Hazardous agent (meets NIOSH 2016 criteria). This medication is not on the NIOSH (2016) list; however, it meets the criteria for a hazardous drug. Drugs are classified as hazardous based on their properties; the properties of a hazardous drug include one or more of the following characteristics: carcinogenic, teratogenic (or other developmental toxicity), reproductive toxicity, organotoxic at low doses, genotoxic, and/or new agents with structural or toxicity profiles similar to existing hazardous agents.

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. NIOSH recommends single gloving for administration of intact tablets or capsules (NIOSH 2016).

**Storage/Stability**
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Store in the original package to protect from moisture.

**Mechanism of Action**
Midostaurin is a tyrosine kinase inhibitor which inhibits multiple receptors, such as wild type FLT3, FLT3 mutant kinases ITD and TKD, KIT (wild type and D816V mutant), PDGFRα/β, VEGFR2, and members of the serine/threonine protein kinase C (PKC) family.

Midostaurin inhibits FLT3 receptor signaling and cell proliferation, and induces apoptosis in ITD- and TKD- mutant expressing leukemic cells, as well as in cells overexpressing wild type FLT3 and PDGFR. It also may inhibit KIT signaling, cell proliferation, and histamine release (and induces apoptosis) in mast cells.