Rydapt (midostaurin)

NEW PRODUCT SLIDESHOW

MPR

Introduction

- **Brand name:** Rydapt
- **Generic name:** Midostaurin
- **Pharmacological class:** Kinase inhibitor
- **Strength and Formulation:** 25mg; capsules
- **Manufacturer:** Novartis Pharmaceuticals
- **How supplied:** Carton—56, 112
- **Legal Classification:** Rx

RYDAPT

Indications

- Newly diagnosed acute myeloid leukemia (AML) in adults who are FLT3 mutation positive in combination with standard cytarabine and daunorubucin induction + cytarabine consolidation
- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL)

Limitations of Use

- **Not for use** as single-agent induction therapy for AML

Dosage & Administration

- Swallow whole
- Take with food approx. 12hrs apart
- Give prophylactic antiemetics prior to initiation
- **AML:** 50mg twice daily on Days 8–21 of each induction cycle with cytarabine and daunorubicin, and on Days 8–21 of each consolidation cycle with high-dose cytarabine

Dosage & Administration

- **ASM, SM-AHN, MCL:** 100mg twice daily until disease progression or unacceptable toxicity
- Dose modifications: see full labeling

Considerations for Special Populations

- **Pregnancy:** Exclude status within 7 days prior to initiation
- **Nursing mothers:** Not recommended during and for ≥4 months after last dose
- **Pediatric:** Not established
- **Elderly:** Use caution

Warnings/Precautions

- **For ASM, SM-AHN, and MCL:** Monitor for toxicity at least weekly for first 4 weeks, then every other week for next 8 weeks, and monthly thereafter
- **Discontinue** if low ANC, platelet count, or hemoglobin persists >21 days

Warnings/Precautions

- **Interrupt** dose if Grade 3/4 nausea and/or vomiting despite antiemetics or other Grade 3/4 non-hematological toxicities; resume at reduced dose and increase as tolerated (see full labeling)

Warnings/Precautions

- **Both:** monitor for signs/symptoms of interstitial lung disease or pneumonitis; **discontinue** if pulmonary toxicity develops
- Embryo-fetal toxicity
- Females of reproductive potential and males should use **effective contraception** during and for at least 4 months after last dose

Interactions

- Concomitant drugs that prolong QT interval; monitor **EKG** periodically
- **Avoid** concomitant strong CYP3A inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John’s wort)

Interactions

- Potentiated by strong **CYP3A** inhibitors (eg, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, diltiazem, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir and [ombitasvir and/or dasabuvir], posaconazole, ritonavir, saquinavir/ritonavir, tipranavir/ritonavir, troleandomycin, voriconazole)
  - Consider alternatives; if co-administration needed, monitor (esp. first week) for increased adverse reactions

Adverse Reactions: AML

- Febrile neutropenia
- Nausea
- Mucositis
- Vomiting
- Headache
- Petechiae
- Musculoskeletal pain
- Epistaxis
- Device-related infection
- Hyperglycemia
- Upper respiratory tract infection

Adverse Reactions: ASM, SM-AHN, MCL

- Diarrhea
- Nausea
- Vomiting
- Edema
- Abdominal pain
- Musculoskeletal pain
- Constipation
- Pyrexia
- Headache
- Fatigue
- Upper respiratory tract infection
- Dyspnea
- Pulmonary toxicity
- Infertility

Mechanism of Action

- Midostaurin is a tyrosine kinase inhibitor that blocks the activity of wild type FLT3, FLT3 mutant kinase (ITD and TKD), KIT, PDGFRα/β, VEGFR2, and PKC members
- The inhibition of the FLT3 receptor signaling prevents cell proliferation and induces apoptosis in leukemic cells
- It also inhibits KIT signaling, cell proliferation and histamine release and induces apoptosis in mast cells

Clinical Studies

- **Study 1** (n=717) was a randomized, double-blind, placebo-controlled trial in patients with newly diagnosed FLT3-mutated AML receiving Rydapt + chemotherapy vs. placebo

Clinical Studies

- Patients received either Rydapt 50mg twice daily or placebo with food on Days 8–21 in combination with daunorubicin/cytarabine for up to 2 cycles of induction and high dose cytarabine for up to 4 cycles of consolidation, followed by continuous Rydapt or placebo for up to 12 additional 28-day cycles

Clinical Studies

- The efficacy endpoint was overall survival (OS), measured from date of randomization until death by any cause
- Follow-up was approximately 3.5 years

Clinical Studies

- Rydapt + chemotherapy was superior to placebo + chemotherapy in **OS** (HR 0.77; 95% CI: 0.63, 0.95; *P*=0.016)
- Event-free survival **(EFS)** was statistically and significantly improved with Rydapt + chemotherapy vs. placebo + chemotherapy (8.2 vs. 3.0 months, HR 0.78, 95% CI: 0.66, 0.93; *P*=0.005)

Clinical Studies

- A secondary analysis of EFS (defined as failure to obtain CR at any time during induction, or relapse, or death) showed a greater median EFS for Rydapt + chemotherapy vs. placebo + chemotherapy (10.6 vs. 5.6 months, HR 0.72, 95% CI: 0.61, 0.86)

Clinical Studies

- **Study 2** (n=116) was a single-arm, open-label, multicenter trial evaluating the use of Rydapt as monotherapy in ASM, SM-AHN, MCL

Clinical Studies

- Patients received Rydapt 100mg twice daily in 28-day cycles until disease progression or until intolerable toxicity
- Efficacy was determined by confirmed complete remission (CR) plus incomplete remission (ICR) by 6 cycles of Rydapt

Clinical Studies

- The estimated median follow-up for duration of response was 35.4 months overall
  - The median duration of CR + ICR was not reached among patients evaluated (95% CI: 24.1 months, NE [not estimated]; range 6.6+, 65.8+)

Clinical Studies

- **Study 3** (n=26) was a single-arm, multicenter, open-label trial of patients with advanced SM
- Patients received Rydapt 100mg twice daily with food

Clinical Studies

- Of the 17 patients with **SM-AHN**, 9 achieved a major response and 1 achieved a partial response by Cycle 2
  - The effect was sustained for at least 8 weeks
- Of the 6 patients with **MCL**, 1 achieved a partial response and 1 achieved major response

Clinical Studies

- Duration of response ranged from 3.4+ to 79.2+ months for SM-AHN and from 28.6+ to 32.1+ months for MCL
  - Median duration of response for either group had not been reached

- For more clinical trial data, see full labeling

New Product Monograph

- For more information view the product monograph available at:

http://www.empr.com/rydapt/drug/34681/