EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Rydapt® (midostaurin capsules – Novartis)

TAC APPROVAL DATE: 02/06/2019

OVERVIEW

Rydapt is a tyrosine kinase inhibitor (TKI) indicated in combination with standard cytarabine + daunorubicin induction and cytarabine consolidation chemotherapy, for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are FMS-like tyrosine kinase 3 (*FLT3*) mutation-positive, as detected by an FDA-approved test.[1] Rydapt is not indicated as a single-agent induction therapy for the treatment of patients with AML. Rydapt is also indicated for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

In patients with AML, therapy should be selected based on the presence of *FLT3* mutation positivity as detected by an FDA-approved test.[1] The recommended dose of Rydapt for patients with AML is 50 mg orally twice daily (BID) with food on Days 8 to 21 of each cycle of induction with cytarabine + daunorubicin and on Days 8 21 of each cycle of consolidation with high-dose cytarabine. In the pivotal trial for Rydapt in *FLT3*-positive AML, Rydapt was administered as a single agent with Rydapt beyond induction and consolidation.[1-3] In ASM, AM-AHN, and MCL, the recommended dose of Rydapt is 100 mg orally BID with food.[1] Treatment is continued until disease progression or unacceptable toxicity occurs. Dose modifications of Rydapt in patients with ASM, SM-AHN, and MCL recommended.

AML

FLT3 Mutation

The prognosis of AML is worse for patients with *FLT3* mutations which comprise approximately 30% to 40% of AML cases.[4] Two major classes of activating *FLT3* mutations have been identified in patients with AML which include the ITD and TKD point mutations. *FLT3*/ITD mutations occur in approximately 30% of cases and are more common than *FLT3*/TKD mutations, which occur in approximately 10% of patients.

General Treatment of AML

Treatment of acute leukemia is divided into induction chemotherapy and post-remission (consolidation) therapy.[4] Most initial treatment decisions for AML are based on age (≥ 60 years of age vs. < 60 years of age), history of prior myelodysplasia or cytotoxic therapy, and performance status. The standard induction chemotherapy used for the treatment of AML (in patients < 60 years of age) consists of cytarabine and an anthracycline (either daunorubicin or idarubicin) administered via intravenous infusion (IV) infusion; Rydapt is the first oral targeted therapy indicated for *FLT3*-mutated AML. Many different therapies are recommended.

Guidelines

The Comprehensive Cancer Network (NCCN) guidelines on AML (version 1.2019 – January 18, 2019), recommend Rydapt + IV chemotherapy among the treatment options for induction, re-induction, and post-remission therapy.[4] For treatment indication for patients < 60 years of age, a recommended regimen

includes standard-dose cytarabine (200 mg/m^2 continuous infusion) x 7 days + daunorubicin (60 mg/m^2) x 3 days + Rydapt (50 mg Q12H) on Days 8 to 21 in FLT3-mutated AML (category 2A). It was noted that while Rydapt was not FDA-approved for maintenance therapy, the pivotal trial was designed for consolidation and maintenance Rydapt for a total of 12 months. After standard-dose cytarabine induction/re-induction in patients < 60 years of age, treatment is based on the results of follow-up bone marrow biopsy. In patients with significant residual disease without hypocellular marrow a recommended regimen includes standard-dose cytarabine + daunorubicin + Rydapt. In patients with significant cytoreduction, the guidelines recommend various regimens including standard-dose cytarabine + daunorubicin + Rydapt. In patients < 60 years of age with intermediate-risk cytogenetics and/or molecular abnormalities, or treatment-related disease other than core binding factor and/or poor risk cytogenetics and/or molecular abnormalities, an option cited is high-dose cytarabine (HiDAC) 1.5 to 3 g/m^2 over 3 hours once every 12 hours on Days 1, 3, 5, or 1, 2, 3 with Rydapt 50 mg once every 12 hours on Days 8 to 21 (FLT3-mutatated AML. Patients ≥ 60 years of age who are candidates for intensive remission induction therapy, for those with intermediate risk cytogenetics and FLT3 mutant, cytarabine + daunorubicin _ In patients ≥ 60 years of age, after standard-dose cytarabine one of the recommended regimens is standard-dose cytarabine + daunorubicin + Rydapt. Post-remission therapy in patients ≥ 60 years of age is based on the type of prior therapy received. For patients who previously received intensive therapy, and who are in remission with a complete response one cited regimens includes intermediate-dose cytarabine + Rydapt.

Systemic Mastocytosis (SM)

Mastocytosis describes a rare group of disorders that are caused by too many mast cells in the body.[4-10] c-Kit mutations are implicated in some types of mastocytosis, including SM.[9] There are four major subtypes of SM: indolent SM (ISM), SM-AHN, ASM, and MCL.[8]

The prognosis of ASM is highly variable, with a median survival of 3.5 to 7 years depending on the study. The only definitive therapy for ASM remains hematopoietic stem cell transplant (HSCT).[7] In general, the prognosis and treatment of SM-AHN is governed by the associated hematologic disorder while controlling the symptoms of mastocytosis. In SM-AHN, HSCT confers the greatest survival benefit in all forms of advanced SM, with a 3-year survival probability of 74% according to a large global retrospective study. The prognosis of SM-AHN remains poor, with a median survival estimated to be 2 to 4.4 years, depending on the study. MCL is by far the most aggressive form of SM, with median survival of approximately 6 months. HSCT offers a potentially curative role in appropriate patients with MCL, yet reports have failed to demonstrate reproducible evidence of durable eradication of the disease.

There are no nationally-recognized guidelines for the treatment of SM.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Rydapt. Because of the specialized skills required for evaluation and diagnosis of patients treated with Rydapt approval requires Rydapt to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Rydapt is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Acute Myeloid Leukemia (AML).** Approve for 3 years if the patient meets the following criteria (A and B)
   - **A)** The patient is *FLT3*-mutation positive AML as detected by an approved test; AND
   - **B)** The patient is receiving Rydapt in one of the following settings (i, ii, iii, or iv):
     - i. Induction therapy in combination with cytarabine and daunorubicin; OR
     - ii. After standard-dose cytarabine induction/reinduction, along with cytarabine and daunorubicin; OR
     - iii. Post remission or consolidation therapy in combination with cytarabine; OR
     - iv. Maintenance therapy.

2. **Aggressive Systemic Mastocytosis (ASM).** Approve for 3 years.

3. **Systemic Mastocytosis Associated with Acute Hematologic Neoplasm (SM-AHN).** Approve for 3 years.

4. **Mast Cell Leukemia (MCL).** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Rydapt has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Rydapt® capsules [prescribing information]. East Hanover, NJ: Novartis; June 2018.
2. Stone RM, Mandrekar S, Laumann K, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with FLT3 mutation. *N Engl J Med*. 2017;377:454-464.
3. The NCCN Acute Myeloid Leukemia Clinical Practice Guidelines in Oncology (Version 1.2019). © 2019 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 29, 2019.
4. Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. *Am J Hematol*. 2018 Dec 8. [Epub ahead of print].
5. Gotlib J, Kluin-Nelemans. HC, George TI, et al. Efficacy and safety of midostaurin to advanced systemic mastocytosis. *N Engl J Med*. 2016;374(26): 2530-2541
6. DeAngelo DJ, George TJ Linder A, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. *Leukemia*. 2018;32:470-478.
7. Van Anrooij B, Oude Elberink JNG, Span LF, et al. Midostaurin in indolent systemic mastocytosis patients: an open-label phase 2 trial. *J Allergy Clin Immunol*. 2018;142(3):1006-1008.
8. Kim ES. Midostaurin: first global approval. *Drugs*. 2017;77:2151-1259.
9. Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. *Br J Haematol*. 2018;180(1):11-23.
10. Kasamon Y, Ko CW, Subramaniam S, et al. FDA approval summary: midostaurin for the treatment of advanced systemic mastocytosis. *Oncologist*. 2018;23:1511-1519.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
New Policy	--	05/24/2017
Annual revision	No criteria changes	07/11/2018
Early annual revision	The following criteria were added: the patient is receiving Rydapt in one of the following settings: 1) induction therapy in combination with cytarabine and daunorubicin; 2) after standard-dose cytarabine induction/reinduction, along with cytarabine and daunorubicin; 3) post-remission or consolidation therapy in combination with cytarabine; OR 4) maintenance therapy.	02/06/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.