CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Rydapt®

GENERIC NAME
Midostaurin

MANUFACTURER
Novartis Pharmaceuticals Corporation

DATE OF APPROVAL
April 28, 2017

PRODUCT LAUNCH DATE
April 28, 2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)

- Treatment of newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation positive as detected by an FDA-approved test, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
  Limitations of Use: Rydapt is not indicated as a single-agent induction therapy for the treatment of patients with AML.

- Treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL)

OFF-LABEL USES
Not applicable

CLINICAL EFFICACY [1]
Acute Myeloid Leukemia:[2]
Treatment of AML is divided into induction and consolidation therapy. Obtaining remission is the first step in controlling disease and the goal of induction therapy is to adequately clear the marrow of leukemia cells to allow recovery of normal hematopoiesis. Sixty to 80 percent of adult patients with newly diagnosed AML will attain a complete remission (CR) with intensive induction chemotherapy. However, without additional cytotoxic therapy, virtually all of these patients will relapse within a median of four to eight months. Rydapt is a tyrosine kinase inhibitor used in both induction and consolidation therapy in patients with FTL3 mutation positive disease. FMS-like tyrosine kinase 3 (FTL3) gene encodes a receptor tyrosine kinase involved in hematopoiesis. There are two major classes of activating FLT3 mutations, the internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. FLT3-ITD mutations occur in approximately 30% of cases and are more common than FLT3-TKD mutations that occur in approximately 10% of cases. FLT3-ITD is a negative prognostic factor, resulting in shorter remission durations and poorer survival outcomes compared to wild-type FLT3 pts. The effect of FLT3-TKD on disease prognosis is less clear.

Rydapt was evaluated in a randomized, double-blind, placebo controlled phase 3 trial that included subjects age 18 to 60 years with newly-diagnosed FLT3-mutated AML. [3] Subjects with acute promyelocytic leukemia or therapy-related AML were excluded. Stratification was based on FLT3 mutation status (TKD, ITD with allelic ratio less than 0.7, and ITD with allelic ratio greater than or equal to 0.7). Subjects were randomized 1:1 to receive induction therapy with Rydapt 50 mg PO BID (n=360) or placebo (n=357) on days 8-21 in combination with daunorubicin (60 mg/m^2 daily on Days 1 to 3) /cytarabine (200 mg/m^2 daily on Days 1 to 7) for up to two cycles. Post remission treatment was with Rydapt 50 mg PO BID or placebo on days 8-21 in combination with high dose cytarabine (3 g/m^2 every 12 hours on Days 1, 3 and 5) for up to four cycles. Therapy was continued with Rydapt 50 mg PO BID or placebo according to initial assignment for up to 12 additional 28-day cycles. Patients who proceeded to hematopoietic stem cell transplantation (SCT) stopped receiving study treatment. The primary outcome of the study was overall survival (OS, date of randomization until death by any cause) with a secondary outcome for event free survival (EFS, defined as the earliest of death, relapse, or no complete response within 60 days of the start of induction). Results for the primary outcome of OS corresponded to a HR 0.77; 95% CI 0.63, 0.95, p=0.007 (survival curves plateaued before reaching the median, median survival could not be reliably estimated). The secondary outcome for EFS was a median of 8.0 months for Rydapt plus standard chemotherapy vs 3.0 months for placebo plus standard chemotherapy with HR 0.80 (95% CI 0.67, 0.95, p=0.0044). 402/717

(57%) patients received an allogeneic SCT (Rydapt 58%; Placebo 54%) at any time (177/717 (25%) after the first complete response; Rydapt 27%; Placebo 22%). Median time to allogeneic SCT was similar on each arm (Rydapt 5.0 months; Placebo 4.6; p=0.23). Secondary analyses for OS and EFS censoring at the time of SCT provided similar results. The median follow-up period was 57 months. A summary of the results are displayed in the following table:

	Arm	Median, mos (95% CI)	p-value	5-year Event rate % (95% CI)	HR (95% CI)
OS	M	74.7 (31.5, *)	0.007	50.8 (45.4-55.9)	0.77 (0.63, 0.95)
	P	26.0 (18.5, 46.5)		43.1 (37.6-48.4)	
OS, SCT censored	M	* (*,*)	0.047	62.6 (54.6-69.7)	0.77 (0.56,1.05)
	P	* (36.9, *)		54.9 (46.2-62.8)	
EFS	M	8.0 (5.3, 10.6)	0.0044	26.7 (22.2-31.5)	0.80 (0.67, 0.95)
	P	3.0 (1.9, 5.8)		19.1 (15.1-23.6)	
EFS, SCT censored	M	8.2 (5.5, 10.7)	0.025	24.2 (18.9-29.8)	0.84 (0.70, 1.0020)
	P	3.0 (1.9, 5.8)		21.8 (16.8-27.3)	

*= not attained

Discontinuation due to any adverse reaction occurred in 9% of patients in the Rydapt arm versus 6% in the placebo arm. The most frequent (> 1%) Grade 3/4 adverse reactions leading to discontinuation in the RYDAPT arm was renal insufficiency (1%).

Advanced Systemic Mastocytosis: [4,5]

Systemic mastocytosis (SM) consists of a group of disorders exhibiting excessive mast cell accumulation, typically in bone marrow and other extracutaneous tissues. Patients are classified into one of five clinical subtypes, which differ in clinical presentation, treatment, and prognosis: indolent systemic mastocytosis, smoldering systemic mastocytosis, aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). Patients with ASM, SM-AHN, and MCL have an aggressive clinical course with end organ damage (e.g., cytopenias, liver dysfunction, malabsorption, ascites, large osteolyses with or without pathologic fractures) and significantly shortened survival. Collectively, they are referred to as "advanced systemic mastocytosis." Activating mutations of KIT, a receptor tyrosine kinase, in mast cells are present in approximately 90% of adults with SM (most commonly the D816V mutation) and lead to enhanced mast cell survival and accumulation and may lower the cells' activation threshold. Tyrosine kinase inhibitors are used for initial therapy in ASM, SM-AHN, and MCL, although their ability to inhibit wild-type or mutated KIT varies. In addition to Rydapt, imatinib is approved for the treatment of ASM without D816V c-Kit mutation as determined by an approved test (or c-Kit mutational status unknown) in adults, however this indication is only applicable in approximately 10% of patients.

CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

Rydapt was evaluated in a multicenter, open-label, single-arm phase 2 study in patients 18 years or older with ASM, SM-AHN, or MCL according to WHO criteria and ECOG 0-3. [6] Patients were excluded if they received 3 or more treatments for mastocytosis, cardiac ejection fraction <50%, serum creatinine > 2.0 mg/dL, hepatic transaminases > 2.5 x upper limit of normal (ULN) or > 5 x ULN if disease-related, total bilirubin > 1.5 x ULN or > 3 x ULN if disease-related, or QTc > 450 msec. The study included 116 patients, 89 patients with measurable clinical findings (C-findings) and were evaluable for response – ASM (n=16), SM-AHN (n=57), MCL (n=16). Patients received Rydapt 100 mg PO BID in 28-day continuous cycles. The primary outcome was best overall response that occurred in the first six 4-week treatment cycles and was maintained for at least 8 weeks. Overall response rate represents the percentage of patients whose best overall response was a:

- Major response (defined as complete resolution of ≥1 C-finding); or
- Partial response (defined as >50% improvement in ≥1 C-finding [good partial response] or as >20% to ≤50% improvement in ≥1 C-finding [minor partial response])

C-findings included:

- Cytopenia(s): Absolute neutrophil count < 1000/μL or hemoglobin < 10 g/dL or platelets < 100,000/μL
- Hepatomegaly with ascites and/or impaired liver function
- Palpable splenomegaly with hypersplenism
- Malabsorption with hypoalbuminemia and weight loss
- Skeletal lesions: large-sized osteolyses or severe osteoporosis causing pathologic fractures
- Life-threatening organopathy in other organ systems that is definitively caused by an infiltration of the tissue by neoplastic mast cells

Secondary outcomes included overall survival, progression-free survival, duration of response. The results are displayed in the following table:

Table: Best Overall Response to Midostaurin in the Primary Efficacy Population

Variable	Any Subtype of Advanced Systemic Mastocytosis (N = 89)	Aggressive Systemic Mastocytosis (N = 16)	Systemic Mastocytosis with an AHN (N = 57)	Mast-Cell Leukemia (N = 16)
Major or partial response as best overall response				
Patients with response — no.	53	12	33	8
Overall response rate (95% CI)	60 (49–70)	75 (48–93)	58 (44–71)	50 (25–75)
Duration of response — mo				

Median	24.1	NR	12.7	NR
95% CI	10.8–NE	24.1–NE	7.4–31.4	3.6–NE

Median Overall Survival:

SM Subgroup	Median OS (95% CI), months	1-Year OS	2-Year OS	3-Year OS
ASM (n=16)	NR (28.7-NE)	93 (61-99)	86 (55-96)	65 (18-90)
SM-AHN (n=57)	20.7 (16.9-44.4)	72 (58-82)	49(34-63)	44(27-59)
MCL (n=16)	9.4 (7.5-NE)	47 (22-69)	26 (6-54)	26 (6-54)

Among the primary efficacy population, 31 (34.8%) discontinued due to progressive disease. Among the primary efficacy population, 18 (20.2%) discontinued due to adverse events, 11 of which were suspected to be drug related.

CONTRAINDICATIONS
Hypersensitivity to midostaurin or any of the excipients

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
- Strong CYP3A4 Inhibitors: Strong CYP3A4 inhibitors may increase exposure to midostaurin and its active metabolites.
- Strong CYP3A4 Inducers: Avoid concomitant use as strong CYP3A4 inducers decrease exposure to midostaurin and its active metabolites.

ADVERSE REACTIONS
- AML: The most common adverse reactions occurring in more than 20% of patients and 5% or more than placebo included: nausea, vomiting, headache, petechiae, device-related infection, and upper respiratory tract infection.
- ASM, SM-AHN, or MCL: The most common adverse reactions (≥ 20%) were nausea, vomiting, diarrhea, edema, musculoskeletal pain, abdominal pain, fatigue, upper respiratory tract infection, constipation, pyrexia, headache, and dyspnea.

DOSAGE AND ADMINISTRATION
AML: 50 mg orally twice daily with food
ASM, SM-AHN, and MCL: 100 mg orally twice daily with food

CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

PRODUCT AVAILABILITY
Capsules: 25 mg

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Imatinib (Gleevec)	**Aggressive systemic mastocytosis:** 400 mg PO QD If clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα: 100 mg PO QD	Only indicated in ASM without the D816V c-Kit mutation, or if Kit mutation status is unknown in patients with ASM not responding satisfactorily to other therapies (e.g.,

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):
  - i) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes.
    - (1) For acute myeloid leukemia, Rydapt is only indicated in patients with the FLT3 mutation and in combination with standard induction and consolidation chemotherapy (e.g. cytarabine and daunorubicin)
  - ii) Recommended utilization management tool(s):
    - (1) ☒ Prior authorization

Product Comparison

Acute myeloid leukemia:

- Rydapt is the only available therapy for FLT3 mutation positive disease (Not scored)

Advanced systemic mastocytosis:

- CPAC score: 69 vs. Gleevec – Modes benefits over current therapy
- For KIT D816V mutation positive disease, it would not be clinically appropriate to require a trial of Gleevec prior to Rydapt.
- For KIT D816V mutation negative or unknown, it would be clinically appropriate to provide equal access to Gleevec and Rydapt.

REFERENCES

[1] Rydapt [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2017.
[2] NCCN Guidelines: Acute Myeloid Leukemia. Version 1.2017. Updated February 24, 2017. Accessed May 10, 2017.
[3] Stone RM, Mandrekar S, Sanford BLet al. The Multi-Kinase Inhibitor Midostaurin (M) Prolongs Survival Compared with Placebo (P) in Combination with Daunorubicin (D)/Cytarabine (C) Induction (ind), High-Dose C Consolidation (consol), and As Maintenance (maint) Therapy in Newly Diagnosed Acute Myeloid Leukemia (AML) Patients (pts) Age 18-60 with FLT3 Mutations (muts): An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance]). Blood 2015. 126 (23):6.
[4] The Mastocytosis Chronicles: Special Edition for Health Care Professionals 2017. The Mastocytosis Society. Available at: https://tmsforacure.org/wp-content/uploads/TMS-Special-Edition-for-Health-Care-Professionals-2017.pdf. Accessed May 2017.
[5] Akin C, Gotlib J. Systemic mastocytosis: Managmentment and prognosis. UpToDate. Updated February 23, 2017. Accessed May 8, 2017.
[6] Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and Safety of Midostaurin in Advanced Sytemic Mastocytosis. NEJM 2016; 374: 2530-41.