PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrRYDAPT®

Midostaurin capsules

25 mg

Antineoplastic agent

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RECENT MAJOR LABEL CHANGES

Warning and Precautions, Pediatrics (< 18 years of age)	[11/2020]
Dosage and Administration, Pediatrics (< 18 years of age)	[11/2020]

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^{Pr}RYDAPT®

Midostaurin capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsule 25 mg	All-rac-α-tocopherol (vitamin E), corn oil mono-di-triglycerides, ethanol anhydrous, gelatin, glycerol, iron oxide red, iron oxide yellow, macrogol 400, macrogolglycerol hydroxystearate, purified water, red pharmaceutical ink, titanium dioxide.

INDICATIONS AND CLINICAL USE

RYDAPT is indicated in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for the treatment of adult patients with newly diagnosed FLT3-mutated acute myeloid leukemia (AML).

A validated test is required to confirm the FLT3 mutation status of AML.

RYDAPT is 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).

Pediatrics (< 18 years of age):

Health Canada has not authorized an indication for the use of RYDAPT in the pediatric population. The safety and efficacy of RYDAPT in pediatric patients have not been established. (see WARNINGS AND PRECAUTIONS, *Special Populations*, DOSING AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY).

Geriatrics:

Clinical studies in AML with RYDAPT did not include sufficient numbers of patients aged 60 years and over to determine whether they respond differently from younger patients (see WARNINGS AND PRECAUTIONS, *Special Populations*).

No overall differences in effectiveness were observed between the patients aged 65 and over compared with younger patients in ASM, SM-AHN and MCL studies (see WARNINGS AND PRECAUTIONS, *Special Populations*).

CONTRAINDICATIONS

RYDAPT is contraindicated in patients with hypersensitivity to midostaurin or to any of the excipients.

WARNINGS AND PRECAUTIONS

General

Treatment with RYDAPT should be initiated by a physician experienced in the use of anticancer therapies.

Drug-Drug Interactions
Concomitant use of RYDAPT with drugs that strongly inhibit CYP3A4 can increase midostaurin exposure. Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicity, especially during the first week of RYDAPT administration in each cycle of chemotherapy (see DRUG INTERACTIONS).

Concomitant use of RYDAPT with drugs that strongly induce CYP3A4 can decrease midostaurin exposure. Concomitant treatment with strong CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John's Wort) should be avoided (see DRUG INTERACTIONS).

Cardiovascular

QTc Interval Prolongation
An increased frequency of QT prolongation was noted in patients treated with RYDAPT (see ADVERSE REACTIONS, ECG Findings). Many drugs that cause QTc prolongation are suspected to increase the risk of torsade de pointes. Particular care should be exercised when administering RYDAPT to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug. Caution should be observed if RYDAPT is administered concomitantly with other QTc interval-prolonging drugs (see DRUG INTERACTIONS).

Cardiac dysfunction
Patients with symptomatic congestive heart failure were excluded from clinical studies. In clinical studies with RYDAPT 100 mg twice daily (BID), events of cardiac failure, some of which were fatal, and decreases in left ventricular ejection fraction (LVEF) occurred. Patients should be assessed for signs and symptoms of heart failure at baseline and periodically during treatment with RYDAPT. In patients at risk, RYDAPT should be used with caution and patients

should be closely monitored by assessing LVEF when clinically indicated (at baseline and during treatment).

Hematologic

Neutropenia / Infections
Neutropenia has occurred in patients receiving RYDAPT (see ADVERSE REACTIONS). Severe neutropenia (ANC less than 0.5 x 10^9/L) was generally reversible by withholding RYDAPT until recovery or discontinuation in the ASM, SM-AHN and MCL studies. White blood cells (WBCs) should be monitored regularly, especially at treatment initiation.

In ASM, SM-AHN, and MCL studies, on-treatment deaths unrelated to the underlying malignancy occurred in 15 patients (11%), most commonly from infection (sepsis or pneumonia).

In patients who develop unexplained severe neutropenia, treatment with RYDAPT should be interrupted until ANC is greater than or equal to 1.0 x 10^9/L in patients with AML or 1.5 x 10^9/L in patients with ASM, SM-AHN and MCL, as recommended in Tables 5 and 6. RYDAPT should be discontinued in patients who develop recurrent or prolonged severe neutropenia that is suspected to be related to RYDAPT (see DOSAGE AND ADMINISTRATION, Dose modifications).

Any active serious infections should be under control prior to starting treatment with RYDAPT monotherapy. Patients should be monitored for signs and symptoms of infection, including any device-related infections, and if a diagnosis of infection is made, appropriate treatment should be instituted promptly, including as needed, the discontinuation of RYDAPT (see DOSAGE AND ADMINISTRATION, Dose modifications).

Monitoring and Laboratory Tests

WBCs should be monitored regularly, especially at treatment initiation (see WARNINGS AND PRECAUTIONS, Hematologic).

Patients should be monitored for signs and symptoms of infection, including any device-related infections, at baseline and periodically during treatment with RYDAPT (see WARNINGS AND PRECAUTIONS, Hematologic).

Patients should be assessed for signs and symptoms of heart failure at baseline and periodically during treatment with RYDAPT. In patients at risk, RYDAPT should be used with caution and patients should be closely monitored (at baseline and during treatment). Electrocardiogram recordings should be performed at baseline and periodically during treatment (see WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, ECG Findings).

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis at baseline and periodically during treatment with RYDAPT (see WARNINGS AND PRECAUTIONS, Respiratory, and DOSAGE AND ADMINISTRATION, Dose modifications).

Respiratory

Pulmonary toxicity

Interstitial lung disease (ILD) and pneumonitis, some of which have been fatal, have occurred in patients treated with RYDAPT. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and RYDAPT should be interrupted in patients who experience pulmonary symptoms indicative of ILD/pneumonitis which are ≥Grade 3 (NCI CTCAE) and resumed at the same dose when infiltrate resolves to Grade ≤1 (NCI CTCAE) (see DOSAGE AND ADMINISTRATION, Dose modifications).

Sexual Health

Reproduction

Pregnancy testing: Sexually-active females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with RYDAPT.

Contraception: Females of reproductive potential should be advised of the potential risk to the fetus. Sexually-active females of reproductive potential should use effective contraception (methods that result in less than 1% pregnancy rates) when using RYDAPT and for at least 4 months after stopping treatment with RYDAPT. It is unknown whether RYDAPT may reduce the effectiveness of hormonal contraceptives; therefore, females using hormonal contraceptives should add a barrier method of contraception.

Male Patients: Sexually-active males taking RYDAPT should be advised to use a condom during intercourse with females of reproductive potential or pregnant women and for at least 4 months after stopping treatment with RYDAPT to avoid conception or embryo-fetal harm.

Fertility

There are no data on the effect of RYDAPT on human fertility. Based on findings in animals, RYDAPT may impair fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible (see TOXICOLOGY, Fertility, Reproductive and Developmental Toxicity).

Special Populations

Patients with renal impairment

Clinical experience in patients with severe renal impairment is limited. No data are available in patients with end-stage renal disease (see ACTION AND CLINICAL PHARMACOLOGY, *Special Populations and Conditions*).

Patients with hepatic impairment

Patients with total bilirubin ≥ 2.5 × upper limit of normal were excluded from studies with RYDAPT in combination with chemotherapy. The ASM, SM-AHN, and MCL studies excluded patients with serum creatinine > 2.0 mg/dL, hepatic transaminases > 2.5 × upper limit of normal

(ULN) or > 5 × ULN if disease-related, total bilirubin > 1.5 x ULN or > 3 × ULN if disease-related. No study has been completed in patients with severe (Child-Pugh C) hepatic impairment. (see ACTION AND CLINICAL PHARMACOLOGY, *Special Populations and Conditions*).

Pregnant Women

RYDAPT can cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits demonstrated that midostaurin caused embryo-fetal toxicity. An increase in late embryo-fetal deaths, a reduction in fetal weight and reduced skeletal ossification were observed in rats and rabbits following prenatal exposure to midostaurin at concentrations over 50–fold below the exposure in humans at the recommended dose of 50 mg twice daily based on AUC. RYDAPT should not be used in women who are pregnant or contemplating pregnancy.

Nursing Women

It is unknown whether midostaurin or its active metabolites are excreted in human milk. There are no data on the effects of RYDAPT on the breastfed child or the effects of RYDAPT on milk production. Studies show that orally administered midostaurin and its active metabolites pass into the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RYDAPT, a nursing woman should be advised to discontinue breast-feeding during treatment with RYDAPT and for at least 4 months after stopping treatment.

Pediatrics (< 18 years of age)

In a phase 2 study, RYDAPT was investigated in combination with chemotherapy in newly diagnosed pediatric patients with FLT3-mutated AML. Four AML patients were treated with midostaurin; 3 patients with confirmed FLT-3 mutation. Among the three FLT3-mutated AML patients enrolled in the study, two patients (10 and 14 years old) experienced Dose Limiting Toxicities (DLTs) following the second induction cycle with midostaurin in combination with chemotherapy (containing cytarabine; fludarabine and idarubicin). Both patients showed markedly delayed hematological recoveries (i.e. prolonged grade 4 thrombocytopenia lasting for 44 days in the first patient and 51 days in the second patient and grade 4 neutropenia lasting for 46 days in the second patient). In the first induction cycle both patients received midostaurin in combination with cytarabine, etoposide and idarubicin.

Health Canada has not authorized an indication for the use of RYDAPT in pediatric population. (see Dosing And ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY)

Geriatrics

Clinical studies in AML with RYDAPT did not include sufficient numbers of patients aged 60 years and over to determine whether they respond differently from younger patients. There is limited experience with the indicated use of RYDAPT in AML patients aged 60-70 years and no

experience in AML patients above 70 years. In patients aged ≥60 years, RYDAPT should be used only in patients eligible to receive intensive induction chemotherapy with adequate performance status and without significant comorbidities.

Of the 142 patients with ASM, SM-AHN, or MCL clinical studies of RYDAPT, 64 (45%) were aged 65 and over, and 16 (11%) were aged 75 years and over. No overall differences in safety were observed between the patients aged 65 and over compared with younger patients, but greater sensitivity of older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

AML

In the phase III, randomized, double-blind, placebo controlled study of RYDAPT in patients with newly diagnosed FLT3-mutated AML, the most frequent (incidence ≥20%) adverse drug reactions (ADRs) in the RYDAPT plus standard chemotherapy arm were febrile neutropenia, nausea, exfoliative dermatitis, vomiting, stomatitis, headache, petechiae, pyrexia, epistaxis, hyperglycemia, back pain and device related infections. The most frequent Grade 3/4 ADRs (incidence ≥10%) were febrile neutropenia, lymphopenia, device-related infection, and exfoliative dermatitis.

Serious ADRs occurred in 32.3% of patients in the RYDAPT plus standard chemotherapy arm versus 30.1% in the placebo plus standard chemotherapy arm. The most frequent serious ADR in patients in the RYDAPT plus standard chemotherapy arm was febrile neutropenia (16.2%) and this occurred at a similar rate in the placebo arm (15.9%), less frequent serious ADRs (over 2%) include: pyrexia (3.1% vs 4.0%), device-related infection (7.4% vs 4.4%), exfoliative dermatitis (2.6% vs 1.8%), hypotension (2.6% vs 1.3%).

Discontinuation due to any adverse event occurred in 9.2% of patients in the RYDAPT arm versus 6.2% in the placebo arm. The most frequent Grade 3/4 adverse event leading to discontinuation in the RYDAPT arm was exfoliative dermatitis (1.2%).

ASM, SM-AHN, and MCL

In two single-arm, open-label, multicenter studies in patients with ASM, SM-AHN, or MCL, the most frequent ADRs (incidence ≥20%) were nausea, vomiting, diarrhea, peripheral edema, fatigue, constipation, pyrexia and headache. The most frequent Grade 3/4 ADRs (incidence ≥5%) were fatigue, sepsis, pneumonia, febrile neutropenia, diarrhea, dyspnea, nausea and vomiting.

Serious adverse events occurred in 68.3% of patients. The most frequent serious adverse events were pneumonia (7%), sepsis (7%) and diarrhea (5.6%).

Adverse events leading to dose modifications (interruption or adjustment) occurred in 56.3% of

patients. The most frequent adverse events that led to dose modification (incidence ≥5%) were nausea, vomiting, electrocardiogram QT prolonged and neutropenia.

Adverse events that led to treatment discontinuation occurred in 23.9% of patients. The most common adverse events leading to discontinuation (incidence ≥1%) were electrocardiogram QT prolonged, ascites, nausea, vomiting, febrile neutropenia, thrombocytopenia, amylase increased, pleural effusion, and acute myeloid leukaemia.

On-treatment deaths unrelated to the underlying malignancy occurred in 15 patients (11%), most commonly from infection (sepsis or pneumonia), followed by cardiac events.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

AML

The safety evaluation of RYDAPT (50 mg twice daily) in patients with newly diagnosed FLT3-mutated AML is based on a phase III, randomized, double-blind, placebo-controlled study. A total of 717 patients were randomized (1:1) to receive RYDAPT or placebo sequentially (on Days 8 to 21) in combination with standard daunorubicin (60 mg/m^2 on Days 1 to 3) / cytarabine (200 mg/m^2 on Days 1 to 7) induction and high dose cytarabine (3 g/m^2 on Days 1, 3, 5) consolidation, followed by maintenance with continuous RYDAPT or placebo treatment according to initial assignment for up to 12 cycles (28 days/cycle). The overall median duration of exposure was 42 days (range 2 to 576 days) for patients in the RYDAPT plus standard chemotherapy arm versus 34 days (range 1 to 465 days) for patients in the placebo plus standard chemotherapy arm. For the 205 patients (120 in RYDAPT arm and 85 in placebo arm) who entered the maintenance phase, the median duration of exposure was 11 months (16 to 520 days for patients in the RYDAPT arm, and 22 to 381 days in the placebo arm).

Table 1 presents the ADRs reported in the phase-III study in patients with newly diagnosed FLT3-mutated AML. ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. The severity of ADRs was graded based on the Common Terminology Criteria for Adverse Event (CTCAE). Table 2 presents the laboratory abnormalities from the same phase-III study in patients with newly diagnosed FLT3-mutated AML.

Table 1 - Adverse Drug Reactions reported in the pivotal AML clinical study

Adverse drug reactions[4]	All grades	Grades 3/4

	RYDAPT + chemo[3] n=229[1] %	Placebo + chemo[3] n=226[1] %	RYDAPT + chemo[3] n=345[1] %	Placebo + chemo[3] n=335[1] %
Blood and lymphatic system disorders				
Febrile neutropenia	83.4	80.5	83.5	83.0
Petechiae	35.8	27.0	1.2	0.6
Lymphopenia[2]	16.6	18.6	20.0	22.7
Cardiac disorders				
Hypotension	14.4	15.0	5.5	3.0
Sinus tachycardia	9.6	8	1.2	0
Hypertension	7.9	5.8	2.3	0.9
Pericardial effusion	3.5	1.3	0.6	0
Eye disorders				
Eyelid edema	3.1	0.4	0	0
Keratitis	6.6	4.9	0.3	0.6
Gastrointestinal disorders				
Nausea[2]	83.4	70.4	5.8	10.1
Vomiting[2]	60.7	52.7	2.9	4.5
Stomatitis	21.8	14.2	3.5	2.7
Abdominal pain upper	16.6	14.6	0	0.3
Hemorrhoids	15.3	10.6	1.4	0
Anorectal discomfort	7	4	0.9	0
Abdominal discomfort	3.5	0.9	0	0
General disorders and administration site conditions				
Pyrexia	34.5	35.4	3.2	2.7
Catheter-related thrombosis	3.5	1.3	2.0	1.8
Immune system disorders				
Hypersensitivity	15.7	14.2	0.6	1.2
Infections and infestations				
Device related infection	24	17.3	15.7	9.9
Upper respiratory tract infection	5.2	3.1	0.6	0.9
Neutropenic sepsis	0.9	0.4	3.5	0.3
Investigations				
Hyperglycemia[2]	20.1	16.8	7	5.4
Activated partial thromboplastin time prolonged	12.7	8.4	2.6	1.8
Weight increased	6.6	3.1	0.6	0.3
Metabolism and nutrition disorders				
Hyperuricemia	8.3	6.2	0.6	0.6
Musculoskeletal and connective tissue disorders				
Back pain	21.8	15.5	1.4	0.6
Arthralgia	14	8	0.3	0.3
Bone pain	9.6	9.7	1.4	0.3
Pain in extremity	9.6	8.8	1.4	0.6
Neck pain	7.9	4	0.6	0
Nervous system disorders				
Headache	45.9	38.1	2.6	3
Syncope	5.2	4.9	4.6	3
Tremor	3.9	1.8	0	0

Adverse drug reactions[4]	All grades		Grades 3/4	
	RYDAPT + chemo[3] n=229[1] %	Placebo + chemo[3] n=226[1] %	RYDAPT + chemo[3] n=345[1] %	Placebo + chemo[3] n=335[1] %
Psychiatric disorders				
Insomnia	12.2	8	0	0.3
Respiratory, thoracic and mediastinal disorders				
Epistaxis	27.5	23.5	2.6	0.6
Laryngeal pain	11.8	9.7	0.6	0.9
Dyspnea	10.9	12.4	5.5	3.9
Pleural effusion	5.7	3.5	0.9	0.9
Nasopharyngitis	8.7	6.6	0	0
Acute respiratory distress syndrome	2.2	0.4	2.3	0.9
Skin and subcutaneous tissue disorders				
Dermatitis exfoliative	61.6	60.6	13.6	7.5
Hyperhidrosis	14.4	8	0	0
Dry skin	7	5.3	0	0

[1] *For the All Grades ADRs in this table, the incidences are those reported from clinical trial sites outside of North America and incidences reported in the North American sites are not captured here. For trial sites in North America, all grades were collected for 13 pre-specified adverse events. For all other adverse events, only grades 3 and 4 were collected.*

[2] *Higher frequency with RYDAPT observed during maintenance phase, please see paragraph below*

[3] *Chemotherapeutic agents: daunorubicin and cytarabine for induction; high dose cytarabine for consolidation*

[4] *The adverse drug reactions were selected on the basis of overall incidence of AEs and the following criteria were applied for data from Study A2301:*

- *Any grade AE > 2% (7 patients) difference in AE incidence between placebo and midostaurin*
- *Any grade 3 or 4 or suspected AE to study drug > 1% difference in AE incidence between placebo and midostaurin*
- *Any AE leading to discontinuation or an SAE > 0.5% difference in incidence between placebo and midostaurin*
- *Selected AEs, AEs of special interest (standard MedDRA queries) >0.5% difference in incidence between placebo and midostaurin*
- *AEs that occur overall in at least 5 patients in either arm*

A total of 205 patients (120 in RYDAPT arm and 85 in placebo arm) who remained in remission following completion of consolidation continued to receive either single agent RYDAPT or placebo for a median of 11 months (range 0.5 to 17 months) with 69 in the RYDAPT arm and 51 in the placebo arm completing 12 treatment cycles. Adverse drug reactions during the maintenance phase with at least ≥5% difference between the RYDAPT and placebo arms were: nausea (46.4% vs 17.9%), hyperglycemia (20.2% vs 12.5%), vomiting (19% vs 5.4%) and lymphopenia (16.7% vs 8.9%). The most frequent grade 3/4 hematological abnormalities reported in patients during the maintenance phase with RYDAPT were ANC decrease (20.8% vs 18.8 %) and leukopenia (7.5% vs 5.9%). The most frequent grade 3/4 non-hematological abnormalities were ALT increased (9.2% vs 3.5%), AST increased (2.5% vs 0).

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 - Percentage of patients with all Grades and Grade 3 and 4 laboratory abnormalities

	RYDAPT 50 mg twice daily + chemo (n=345)		Placebo + chemo (n=335)	
	All grade %	**Grade 3/4 %**	**All grade %**	**Grade 3/4 %**
Absolute neutrophils decreased	86.7	85.8	88.1	86.9
Hemoglobin decreased	97.4	78.6	98.9	77.6
Platelets decreased	96.2	95.9	94.9	94.3
WBC decreased	95.1	94.8	94.0	93.4
Aspartate aminotransferase (AST) increased	73.9	6.4	65.4	6.0
Alanine aminotransferase (ALT) increased	84.1	19.4	81.5	14.9
Hypercalcemia	6.7	0.6	3.6	0.3
Hypocalcemia	91.3	7.2	91.3	7.8
Hyperkalemia	11.6	0.3	11.6	1.2
Hypokalemia	61.7	13.9	60.9	14.3
Serum Creatinine	9.3	0	9.6	0
Total Bilirubin	52.5	11.0	58.2	13.7
Hypernatremia	20.0	1.2	14.9	1.8
Hyponatremia	66.1	10.4	73.1	8.7

ECG Findings: In the randomized placebo-controlled trial in patients with AML, the proportion of patients with QTc prolongation was higher in patients randomized to midostaurin (N=345) as compared to placebo (N=335).

QTcF >480 ms: 10.1% vs 5.7%

QTcF >500 ms: 6.2% vs 2.6%

QTcF increase from baseline >60 ms: 18.4% vs 10.7%

Adverse events in elderly AML patients

An interim analysis was conducted on 145 patients (99 patients were ≤ 60 years of age; 46 were > 60 to 70 years of age) enrolled into the first cohort of a phase II study. The most frequent adverse events observed across all grades and based on system organ class were blood/lymphatic system disorders (e.g. anemia, febrile neutropenia) and gastrointestinal disorders (e.g. nausea, vomiting). The incidence of adverse events when compared between the younger and older age

groups (≤ 60, >60 to 70 years of age) appear to be similar in general. The frequency of treatment-related severe adverse events (≥ grade 3) and the frequency of serious adverse events were slightly higher in the older age group (85% vs. 80% and 72% vs. 62%, respectively). Although this is an interim analysis, the overall incidence of all treatment related adverse events as well as Grade 3/4 adverse events appear to be consistent with that observed in Study A2301 (see Table 1). The rates of early death were higher in older compared to younger patients (17% and 2%, respectively).

ASM, SM-AHN, and MCL

The safety of RYDAPT (100 mg twice daily with food) as a single agent in patients with ASM, SM-AHN, or MCL was evaluated in 142 patients in two single-arm, open-label, multicenter studies. The median age was 63 (range: 24 to 82), 63% had an ECOG performance status of 0 or 1, and 75% had no hepatic impairment (bilirubin and AST ≤ ULN) at baseline. Patients with QTcF > 450 ms at baseline were excluded from studies. The median duration of exposure to RYDAPT was 11.4 months (range: 0 to 81 months), with 34% treated for ≥ 24 months.

Table 3 presents the frequency category of ADRs based on pooled data from two studies in patients with ASM, SM-AHN, and MCL. ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. Table 4 presents the key laboratory abnormalities based on pooled data from two studies in patients with ASM, SM-AHN, and MCL.

Table 3 - Adverse drug reactions reported in ASM, SM-AHN, and MCL studies

Adverse drug reaction	RYDAPT (100 mg twice daily) N=142	
	All grades %	Grade 3/4 %
Blood and lymphatic system disorders		
Febrile neutropenia	7.7	7.0
Ear and labyrinth disorders		
Vertigo	4.9	0
Gastrointestinal disorders		
Nausea	82	5.6
Vomiting	68	5.6
Diarrhea	51	6.3
Constipation	29	0.7
Dyspepsia	5.6	0
Gastrointestinal hemorrhage	4.2	3.5
General disorders and administration site conditions		
Edema peripheral	35	3.5
Fatigue	31	8.4
Pyrexia	27	4.2
Asthenia	4.9	0.7
Chills	4.9	0
Edema	4.2	0.7

Infections and infestations		
Urinary tract infection	13	2.8
Upper respiratory tract infection	11	1.4
Pneumonia	8.5	7.0
Sepsis	7.7	7.7
Bronchitis	5.6	0
Oral herpes	4.9	0
Cystitis	4.2	0
Sinusitis	4.2	0.7
Erysipelas	3.5	1.4
Herpes zoster	3.5	0.7
Injury, poisoning and procedural complications		
Contusion	6.3	0
Fall	4.2	0.7
Immune system disorders		
Hypersensitivity	2.1	0
Anaphylactic shock	0.7	0.7
Investigations		
Weight increased	5.6	2.8
Nervous system disorders		
Headache	26	1.4
Dizziness	13	0
Disturbance in attention	7	0
Tremor	6.3	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	18	5.6
Cough	16	0.7
Pleural effusion	13	4.2
Epistaxis	12	3.8
Oropharyngeal pain	4.2	0
Vascular disorders		
Hypotension	9.2	2.1
Hematoma	6.3	0.7

Abnormal Hematologic and Clinical Chemistry Findings

Table 4 - Percentage of patients with key laboratory abnormalities in the ASM, SM-AHN, and MCL studies

Key laboratory abnormality	**RYDAPT (100 mg twice daily) N=142**	
	All grade %	**Grade 3/4 %**
Glucose increased*	93.7	19.0
Absolute neutrophils decreased	58.5	26.8
Absolute lymphocyte decreased	73.2	45.7

Aspartate aminotransferase (AST) increased	33.8	2.8
Alanine aminotransferase (ALT) increased	33.1	3.5
Total bilirubin increased	40.1	4.9
Amylase increased	20.4	7.0
Lipase increased	39.4	17.6

**non fasting*

ECG Findings: Evaluation of the notable QTcF from the pooled dataset demonstrated that 6 patients had a post-baseline QTc interval of > 480 ms and 8 patients had an increase of > 60 ms in QTc interval compared to baseline. No patient experienced a QTcF value of > 500 ms.

Description of selected adverse drug reactions

Gastrointestinal disorders

In the ASM, SM-AHN, and MCL patient population 17 (12%) patients had a dose adjustment or interruption for nausea, 13 (9.2%) for vomiting, and 7 (4.9%) for diarrhea. The treatment discontinuation rate was low with 3 (2.1%) patients discontinued for nausea, 2 (1.4%) patients for vomiting, and 1 (0.7%) patient for diarrhea. Most of the events occurred within the first 6 months of treatment and were well managed with supportive prophylactic medication.

DRUG INTERACTIONS

Overview

Midostaurin undergoes extensive hepatic metabolism through CYP3A4 enzymes. Drug interactions were observed when RYDAPT was co-administered with a strong CYP3A4 inhibitor and a strong CYP3A4 inducer. Based on in vitro data, RYDAPT may potentially increase the exposure of co-administered medicinal products primarily cleared by CYP2D6, CYP2E1, glycoprotein (P-gp), breast cancer resistance protein (BCRP) or organic anion transporting polypeptide (OATP)1B1, and decrease the exposure of co-administered medicinal products primarily cleared by CYP2B6 and CYP2C19. The effect of RYDAPT on the exposure of co-administered medicinal products that are substrates of CYP1A2, CYP2C8 or CYP2C9 is uncertain.

Drug-Drug Interactions

<u>Agents that may increase midostaurin plasma concentrations</u>

***CYP3A4 Inhibitors*:** In a study with 36 healthy volunteers, co-administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily on Days 1 to 10) to steady-state with a single dose of RYDAPT (50 mg) on Day 6 led to a significant increase in exposure to midostaurin (C_{max} and AUC_{inf} increased by 1.8- and 10.4-fold, respectively) and the metabolite CGP62221 (AUC_{inf} increased by 3.5-fold).

In a study in patients with AML (n=7), co-administration of the strong CYP3A4 inhibitor

itraconazole (100 mg bid on Days 22 to 28) to steady-state with multiple doses of RYDAPT (100 mg bid on Days 1 to 2 and 50 mg bid on Days 3 to 28) increased steady-state midostaurin C_{min} by 2.09-fold.

Caution is required when concomitantly prescribing RYDAPT with medicinal products that are strong inhibitors of CYP3A4, such as, but not limited to, antifungals (e.g. ketoconazole, itraconazole, voriconazole, posaconazole), certain antivirals (e.g. ritonavir), and macrolide antibiotics (e.g. clarithromycin). Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicity, especially during the first week of RYDAPT administration in each cycle of chemotherapy.

Agents that may decrease midostaurin plasma concentrations

CYP3A4 Inducers: In a study in healthy subjects, co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily on Days 1 to 14) to steady state with a single dose of midostaurin (50 mg) on Day 9 decreased midostaurin C_{max} by 73% and AUC_{inf} by 96%, respectively. Both active metabolites CGP62221 and CGP52421 exhibited a similar pattern.

Concomitant treatment with strong CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John's Wort) should be avoided.

Drugs that may have their plasma concentrations altered by midostaurin

CYP3A4/5 substrates*:* In a study in healthy subjects, midazolam (sensitive CYP3A4 substrate) AUC_{inf} was not affected following 4 days of RYDAPT administration. The clinical relevance of this interaction is unknown as the RYDAPT was administered for only a limited period of time (i.e. 4 days).

Based on in vitro data, midostaurin and its active metabolites can potentially induce and inhibit CYP3A4/5. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4/5 should be used with caution when co-administered with RYDAPT.

CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, P-gp, BCRP or OATP1B1 substrates: Based on in vitro data, midostaurin and its active metabolites are considered to be inhibitors of CYP2D6, CYP2E1, P-gp, BCRP, BSEP or OATP1B1, and may potentially increase the exposure of co-administered medicinal products primarily cleared by CYP2D6, CYP2E1, P-gp, BCRP or OATP1B1.

Based on in vitro data, midostaurin and its active metabolites are considered to be inducers of CYP2B6 and CYP2C19, and may potentially decrease the exposure of co-administered medicinal products primarily cleared by CYP2B6 and CYP2C19.

In vitro, midostaurin and its active metabolites are both inhibitors and inducers of CYP1A2, CYP2C8 or CYP2C9. The clinical effect of RYDAPT on the exposure of co-administered medicinal products that are substrates of these CYPs is unknown.

Medicinal products with a narrow therapeutic range that are substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, P-gp (e.g. paclitaxel), BCRP (e.g. atorvastatin) or OATP1B1 should be used with caution when co-administered with RYDAPT.

QTc Interval-Prolonging Drugs

Caution should be observed if RYDAPT is used concomitantly with other QTc interval-prolonging drugs (See WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, ECG Findings). Drugs that have been associated with QT interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or torsade de pointes:
Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide), Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone), Class 1C antiarrhythmics (e.g., flecainide, propafenone), antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, risperidone), antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline]), opioids (e.g., methadone), macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus), quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin), pentamidine, antimalarials (e.g., quinine, chloroquine), azole antifungals (e.g., ketoconazole, fluconazole, voriconazole), domperidone, 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron), tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib), arsenic trioxide, histone deacetylase inhibitors (e.g., vorinostat), beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Affect Electrolytes

Caution should be observed if RYDAPT is used with drugs that can disrupt electrolyte levels, including, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; proton pump inhibitors.

The above lists of potentially interacting drugs are not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval or decrease electrolytes, as well as for older drugs for which these effects have recently been established.

Drug-Food Interactions

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase midostaurin plasma concentrations and should be avoided.

In healthy subjects, the extent of midostaurin absorption (AUC) was increased by an average of 22% when RYDAPT was co-administered with a standard meal containing 450 calories, about 25% of which came from fat (e.g., turkey breast with sauce, mashed potatoes, and salad). The AUC increased by an average of 59% when co-administered with a high-fat meal containing 1000 calories, about half of which came from fat (e.g., toast with butter, bacon, fried eggs, fried

potatoes, and whole milk). The peak midostaurin concentration (C_{max}) was reduced by 20% with a standard meal and by 27% with a high-fat meal versus on an empty stomach (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Drug-Herb Interactions
Drug-herb interactions have not been studied. St. John's wort (Hypericum perforatum) is an inducer of CYP3A4/5 that may decrease midostaurin plasma concentrations and should be avoided.

Drug-Laboratory Interactions
Drug-laboratory interactions have not been studied.

Drug-Lifestyle Interactions
Drug-lifestyle interactions have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment with RYDAPT should be initiated by a physician experienced in the use of anticancer therapies.

AML
Prior to initiation of treatment with RYDAPT in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy, patients must have confirmation of FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test.

In patients receiving a hematopoietic stem cell transplant (SCT), RYDAPT should be discontinued prior to the conditioning regimen for SCT.

Recommended Dose and Dosage Adjustment

Recommended dose in AML
The recommended dose of RYDAPT is 50 mg twice daily on Days 8 to 21 of each cycle of induction with cytarabine and daunorubicin and on Days 8 to 21 of each cycle of consolidation with cytarabine.

Patients may be given up to 2 cycles of induction therapy with cytarabine and daunorubicin if complete remission is not observed at the end of the first induction cycle. Each induction cycle is a minimum of 24 days in duration. Patients who have residual AML after a second induction cycle should be discontinued from RYDAPT treatment.

Patients in complete remission after induction therapy should be given up to 4 cycles of consolidation therapy with cytarabine. Each consolidation cycle is a minimum of 28 days in

duration and should begin within two weeks following hematologic recovery (ANC ≥ 1000/μL and platelet count ≥ 100,000/μL) but not sooner than 28 days from the beginning of the previous cycle.

Recommended dose in ASM, SM-AHN, and MCL
The recommended starting dose of RYDAPT is 100 mg twice daily.

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

RYDAPT should be taken orally, twice daily at approximately 12 hour intervals. RYDAPT should be taken with food to help prevent nausea (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Prophylactic anti-emetics should be administered in accordance with local medical practice as per patient tolerance.

RYDAPT capsules should be swallowed whole with a glass of water. RYDAPT capsules should not be opened, crushed or chewed.

Dose modifications

Dose modifications in AML
Recommendations for dose modifications of RYDAPT in patients with AML are provided in Table 5.

Table 5 - RYDAPT dose interruption, reduction, and discontinuation recommendations in patients with AML

Criteria	RYDAPT dosing
Grade 3/4 pulmonary infiltrates	Interrupt RYDAPT for the remainder of the cycle. Resume RYDAPT at the same dose when infiltrate resolves to Grade ≤1.
Other Grade 3/4 non-hematological toxicities	Interrupt RYDAPT until toxicities considered at least possibly related to RYDAPT have resolved to Grade ≤2, then resume RYDAPT.

Dose modifications in ASM, SM-AHN, and MCL
Recommendations for dose modifications of RYDAPT in patients with ASM, SM-AHN, and MCL are provided in Table 6.

Table 6 - RYDAPT dose interruption, reduction, and discontinuation recommendations in patients with ASM, SM-AHN, and MCL

Criteria	RYDAPT dosing
ANC less than 1 x 10^9/L attributed to	Interrupt RYDAPT until ANC greater than or

Criteria	RYDAPT dosing
RYDAPT in patients without MCL, or ANC less than 0.5 x 10^9/L attributed to RYDAPT in patients with baseline ANC value of 0.5-1.5 x 10^9/L	equal to 1.5x 10^9/L, then resume RYDAPT at 50 mg twice daily, and if tolerated, gradually increase to 100 mg twice daily. Discontinue RYDAPT if low ANC persists for > 21 days and is suspected to be related to RYDAPT.
Platelet count less than 50 x 10^9/L attributed to RYDAPT in patients without MCL, or platelet count less than 25 x 10^9/L attributed to RYDAPT in patients with baseline platelet count of 25-75 x 10^9/L	Interrupt RYDAPT until platelet count greater than or equal to 50 x 10^9/L, then resume RYDAPT at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily. Discontinue if low platelet count persists for > 21 days and is suspected to be related to RYDAPT.
Hemoglobin less than 8 g/dL attributed to RYDAPT in patients without MCL, or life-threatening anemia attributed to RYDAPT in patients with baseline hemoglobin value of 8 -10 g/dL	Interrupt RYDAPT until hemoglobin greater than or equal to 8 g/dL, then resume RYDAPT at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily. Discontinue if low hemoglobin persists for > 21 days and is suspected to be related to RYDAPT.
Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy	Interrupt RYDAPT for 3 days (6 doses), then resume RYDAPT at 50 mg twice daily, and if tolerated, gradually increase to 100 mg twice daily.
Other Grade 3/4 non-hematological toxicities	Interrupt RYDAPT until event has resolved to ≤ Grade 2, then resume RYDAPT at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily.

ANC: Absolute Neutrophil Count
CTCAE severity: Grade 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

Special populations

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/min). Clinical experience in patients with severe renal impairment (CrCl 15 to 29 mL/min) is limited. No data are available in patients with end-stage renal disease.

Hepatic impairment
No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. No data are available in patients with severe (Child-Pugh C) hepatic impairment. Patients with total bilirubin ≥ 2.5 × upper limit of normal were excluded from studies with RYDAPT in combination with chemotherapy. The ASM, SM-AHN, and MCL study excluded patients with 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.

Pediatric patients (below 18 years)
Health Canada has not authorized an indication for the use of RYDAPT in the pediatric population. RYDAPT should not be used in combination with intensive pediatric AML combination chemotherapy regimens including anthracyclines, fludarabine and cytarabine (see WARNING AND PRECAUTION, *special populations*, and ACTION AND CLINICAL PHARMACOLOGY, *Special Populations and Conditions*)

Geriatric patients
There is limited experience with the indicated used of RYDAPT in AML patients aged 60-70 years and no experience in AML patients above 70 years. In patients aged ≥60 years, RYDAPT should be used only in patients eligible to receive intensive induction chemotherapy with adequate performance status and without significant comorbidities (see WARNINGS AND PRECAUTIONS, *Special Populations*).

Appropriate caution should be used when prescribing to the elderly patients with ASM, SM-AHN, and MCL, as increased vulnerability to drug effect is possible in this patient population (see WARNINGS AND PRECAUTIONS, *Special Populations*).

Missed Dose
If a dose is missed, the dose should not be made up and the patient should only take the next scheduled dose at the scheduled time.

If vomiting occurs, the patient should not take an additional dose of RYDAPT, but should take the next scheduled dose.

OVERDOSAGE

Reported experience with overdose in humans is very limited.

There is no known specific antidote for midostaurin. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated. ECG monitoring is recommended.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Midostaurin inhibits multiple receptor tyrosine kinases, including FLT3 and KIT kinase. Midostaurin inhibits FLT3 receptor signaling and induces cell cycle arrest and apoptosis in leukemic cells expressing internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutant receptors or overexpressing wild type receptors. Midostaurin inhibits both the wild type and D816V mutant KIT, leading to interference with the aberrant signaling of KIT and inhibits mast cell proliferation and survival, and histamine release.

In addition, it inhibits several other receptor tyrosine kinases such as PDGF-R or VEGFR2, as well as members of the serine/threonine kinase family PKC (protein kinase C). Midostaurin binds to the catalytic domain of these kinases and inhibits the mitogenic signaling of the respective growth factors in cells, resulting in growth arrest.

Pharmacodynamics

Midostaurin is a high affinity inhibitor for the receptor tyrosine kinase of FLT3 (Kd of 11 nM) and is equally active against ITD- and TKD-mutated FLT3.

The affinity constant of midostaurin to the wild type receptor tyrosine kinase KIT has been determined as 220 nM and that of the D816V mutant as 7.7 nM.

Two major metabolites have been identified in murine models and humans, i.e. CGP62221 and CGP52421. In proliferation assays with FLT3-ITD expressing cells, CGP62221 showed similar potency compared to the parent compound, whereas CGP52421 was approximately 10 fold less potent.

Pharmacokinetics

Absorption: In humans, the absorption of midostaurin is rapid after oral administration, with T_{max} of total radioactivity observed at 1 to 3 hours post dose under fasting conditions.

In healthy subjects, the extent of midostaurin absorption (AUC) was increased by an average of 22% when RYDAPT was co-administered with a standard meal containing 450 calories, about 25% of which came from fat and the AUC increased by an average of 59% when co-administered with a high-fat meal containing 1000 calories, about half of which came from fat. The peak midostaurin concentration (C_{max}) was reduced by 20% with a standard meal and by 27% with a high-fat meal versus on an empty stomach. The time to reach the peak concentration was also delayed in the presence of a standard meal or a high-fat meal (median T_{max} = 2.5 or 3.0 h, respectively) as compared to fasted dosing (median T_{max} 1.0 h). In clinical studies, midostaurin was administered with a meal, in order to decrease potential nausea and vomiting events. It is recommended that midostaurin is administered to patients with food.

Distribution: Midostaurin has a geometric mean volume of distribution (Vz/F) of 95.2 L.

Midostaurin and its metabolites are distributed mainly in plasma rather than red blood cells. In vitro data showed midostaurin is greater than 98% bound to plasma protein mainly to alpha-1-acid glycoprotein (AGP). It is unknown whether midostaurin can cross the blood brain barrier in human. However, the tissue distribution was investigated using quantitative whole body autoradiography (QWBA) in rats after an intravenous or oral administration of [^{14}C]midostaurin. Radioactivity from [^{14}C]midostaurin in rats was taken up by the pituitary gland and crossed the blood brain barrier, and the highest [^{14}C] concentrations were seen in the frontal cortex.

Metabolism: Midostaurin is primarily metabolized by CYP3A4. The two major active metabolites, CGP62221 (via O-demethylation) and CGP52421 (via hydroxylation), account for 28± 2.7% and 38± 6.6% respectively, of the total plasma exposure (AUC0-168h) after a single 50 mg dose of midostaurin.

Excretion: The median terminal half-lives of midostaurin, CGP62221 and CGP52421 in plasma are approximately 21, 32 and 471 hours. Fecal excretion is the major route of excretion (78% of the dose), and mostly as metabolites (73% of the dose) while unchanged midostaurin accounts for 3% of the dose. Only 4% of the dose is recovered in urine.

Linearity/non-linearity: In general, midostaurin and its metabolites showed no major deviation from dose-proportionality after a single dose in the range of 25 mg to 100 mg. However, there was a less than dose-proportional increase in exposure after multiple doses within the dose range of 50 mg to 225 mg daily. The highest C_{min} and steady-state of midostaurin, CGP62221, and CGP52421 were similar when RYDAPT was administered with food at a dose of 50 mg twice daily or 100 mg twice daily.

Following multiple oral doses, midostaurin displayed time-dependent pharmacokinetics with an initial increase in plasma concentrations during the first week (peak C_{min}) followed by a decline with time to a steady-state after approximately 28 days. The pharmacokinetics of the CGP62221 metabolite showed a similar trend. However, CGP52421 concentrations increased up to 9-fold compared to midostaurin after one month of treatment in AML patients.

Special Populations and Conditions

Pediatrics:
The safety and efficacy of RYDAPT in pediatric patients have not been established.

The pharmacokinetics of midostaurin in pediatric patients were explored in a phase 1 dose escalation monotherapy study with 22 patients (12 aged 0 to 2 years and 10 aged 10 to 17 years) with AML or MLL-gene rearranged acute lymphoblastic leukemia (MLL-rearranged ALL) using a population pharmacokinetic approach. The exposure of midostaurin, CGP62221, or CGP52421 decreased with increasing weight and age at a given mg/m^2 dose.

Geriatrics: Based on a population pharmacokinetic analysis of data from patients with AML, age (20 to 94 years) did not have clinically meaningful effects on the clearance of midostaurin and its active metabolites.

Gender: In population pharmacokinetic analyses, gender did not have clinical meaningful effects on the clearance of midostaurin and its active metabolites. No midostaurin dose adjustment is required based on gender.

Race: There are no differences in the pharmacokinetic profile between Caucasian and Black subjects. Based on the phase I study in healthy Japanese volunteers, pharmacokinetic profiles of midostaurin and its metabolites (CGP62221 and CGP52421) are similar compared to those observed in other pharmacokinetic studies conducted in Caucasians and Blacks. No midostaurin dose adjustment is required based on ethnicity.

Hepatic Insufficiency: A dedicated hepatic impairment study assessed the systemic exposure of midostaurin in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A or B, respectively) and control subjects with normal hepatic function. RYDAPT (50 mg bid) was administered for 6 days followed by 50 mg single dose on Day 7. There was no clinically relevant increase in exposure (AUC) to plasma midostaurin in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. Based on population pharmacokinetic analyses, mild and/or moderate hepatic impairment did not show a significant effect on the pharmacokinetics of midostaurin or its metabolites in patients treated with RYDAPT and the anticipated changes were not deemed to be clinically relevant. No dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. The pharmacokinetics of midostaurin have not been assessed in patients with baseline severe hepatic impairment (Child-Pugh Class C).

Renal Insufficiency: No dedicated renal impairment study was conducted for midostaurin. Population pharmacokinetic analyses were conducted using data from clinical trials in patients treated with RYDAPT. Out of the 321 patients included, 177 patients showed pre-existing mild (n=113), moderate (n=60) or severe (n=4) renal impairment (15 mL/min ≤creatinine clearance [CrCL] <90 mL/min). 144 patients showed normal renal function (CrCL>90 mL/min) at baseline. Based on the population pharmacokinetic analyses, midostaurin clearance was not significantly impacted by mild or moderate renal impairment. There was insufficient data (n=4) for patients with severe renal impairment (CrCl 15 to 29 mL/min). No dosage adjustment is necessary for patients with mild or moderate renal impairment (CrCl ≥30 mL/min).

STORAGE AND STABILITY

Do not store above 30°C. Store in the original package to protect from moisture.

RYDAPT must be kept out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RYDAPT 25 mg capsules for oral administration are pale orange, oblong capsule with red imprint ‘PKC NVR’. Available in blisters, in multipacks of 56 and 112 capsules.

RYDAPT capsules contain 25 mg of midostaurin (from a benzyl alcohol and ethanol solvate form of midostaurin) and the following excipients: All-rac-α-tocopherol (vitamin E), corn oil mono-di-triglycerides, ethanol anhydrous, gelatin, glycerol, iron oxide red, iron oxide yellow, macrogol 400, macrogolglycerol hydroxystearate, purified water, red pharmaceutical ink, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

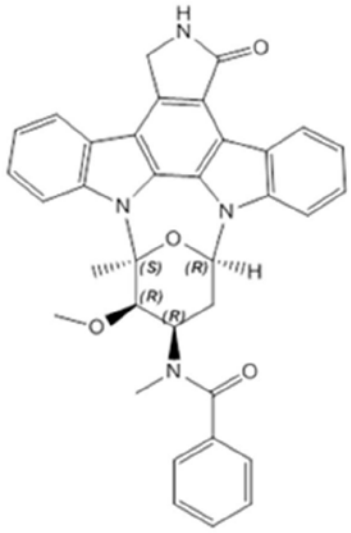
Common name: midostaurin

Chemical name:

Preferred IUPAC name:
N-[(2S,3R,4R,6R)-3-Methoxy-2-methyl-16-oxo-29-oxa-1,7,17-triazaoctacyclo [12.12.2.12,6.07,28.08,13.015,19.020,27.021,26]nonacosa-8,10,12,14,19,21,23,25,27-nonaen-4-yl]-Nmethylbenzamide

CAS:
N-[(9S,10R,11R,13R)-2,3,10,11,12,13-Hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:3′,2′,1′-lm]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl]-Nmethylbenzamide

Molecular formula: $C_{35}H_{30}N_4O_4$ (on solvate-free basis)
Molecular mass: 570.65 (on solvate-free basis)
Structural formula:



Midostaurin is isolated as a crystalline benzyl alcohol and ethanol solvate.

Physicochemical properties:

The drug substance is a white to light yellow or light green powder. The drug substance is

poorly soluble in water (< 0.001 mg/mL). The compound is slightly hygroscopic.

CLINICAL TRIALS

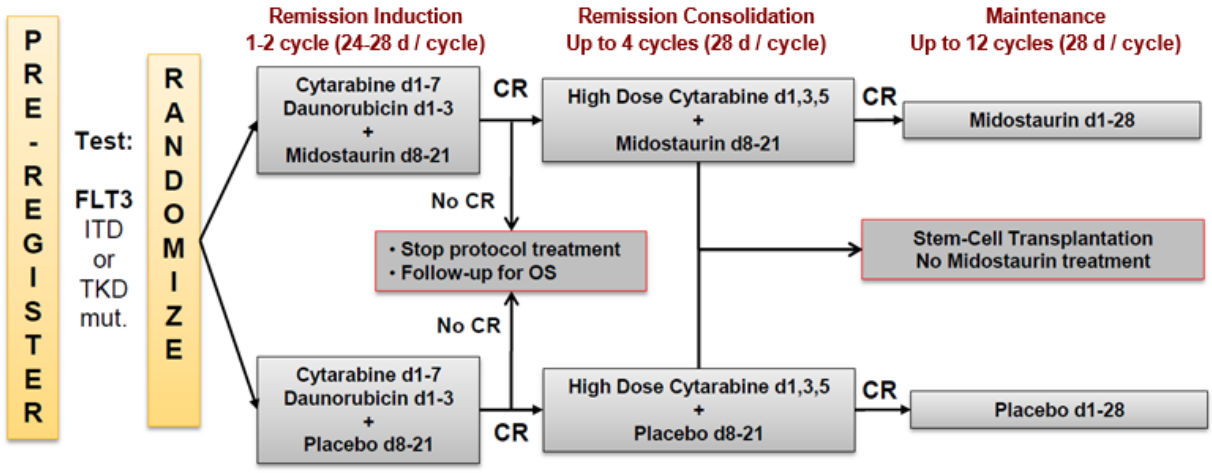
Acute Myeloid Leukemia (AML)

Pivotal phase III study (RATIFY)

Study demographics and trial design

The efficacy and safety of RYDAPT in combination with standard chemotherapy versus placebo plus standard chemotherapy and as single agent maintenance therapy was investigated in 717 patients (18 to 60 years of age) in a randomized, double-blind, phase III study. Patients with newly diagnosed FLT3-mutated AML as determined by a clinical trial assay were randomized (1:1) to receive RYDAPT 50 mg twice daily (n=360) or placebo (n=357) sequentially (Days 8 to 21) in combination with standard 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 of induction and high dose cytarabine (3 g/m^2 every 12 hours on Days 1, 3, 5) for up to four cycles of consolidation, followed by continuous RYDAPT or placebo treatment according to initial assignment for up to 12 additional 28-day cycles as maintenance (see Figure 1). There was no re-randomization at the start of maintenance therapy. Patients who proceeded to hematopoietic stem cell transplant (SCT) stopped receiving study treatment before SCT conditioning regimen.

Figure 1 - Design of pivotal phase III Study



Patients with acute promyelocytic leukemia (M3) or therapy-related AML were excluded. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio <0.7, and ITD with allelic ratio ≥0.7.

The two treatment groups were generally balanced with respect to the baseline demographics of disease characteristics, except that the placebo plus standard chemotherapy arm had a higher percentage of females than in the RYDAPT plus standard chemotherapy arm, and details are shown in Table 4.

Table 7- Study: Demographics and baseline characteristics

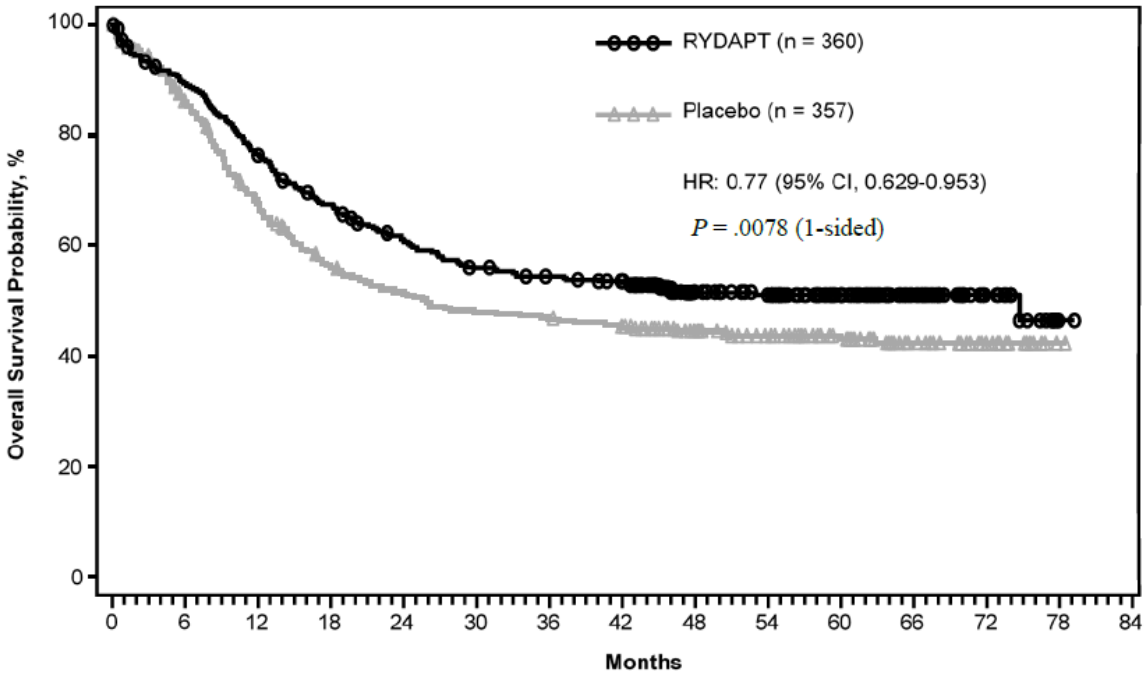
Baseline characteristics	MIDOSTAURIN n=360	PLACEBO n=357
Age (Years)		
Median/Maximum	47.0 / 59	48.0 / 60
Gender -n (%)		
Female	186 (51.7)	212 (59.4)
Male	174 (48.3)	145 (40.6)
ECOG performance status –n (%)		
0 to 2	352 (97.8)	346 (96.9)
3 to 4	8 (2.2)	11 (3.1)
Race -n (%)		
Unknown / Not Reported	195 (54.2)	213 (59.7)
White	147 (40.8)	128 (35.9)
Black or African American	8 (2.2)	9 (2.5)
Other	10 (2.8)	7 (2)
FLT3 mutation status -n (%)		
ITD <0.7	171 (47.5)	170 (47.6)
ITD ≥0.7	108 (30.0)	106 (29.7)
TKD	81 (22.5)	81 (22.7)

ITD: Internal Tandem Duplication. TKD: Tyrosine Kinase Domain.
Note: ITD <0.7, ITD ≥0.7 and TKD are the randomization strata.
ECOG: The Eastern Cooperative Oncology Group

Of the 717 patients, 25% had a second course of induction, 62% initiated at least one cycle of consolidation, 29% initiated maintenance, and 17% completed all 12 planned cycles of maintenance. The overall rate of SCT was 59.4% (214/360) of patient in the RYDAPT plus standard chemotherapy arm versus 55.2% (197/357) in the placebo plus standard chemotherapy arm. Twenty-one percent of all the patients in the study underwent SCT in the first complete remission. All patients were followed for survival.

The primary endpoint of the study was overall survival (OS), measured from the date of randomization until death by any cause. The primary analysis was conducted after a minimum follow-up of approximately 3.5 years after the randomization of the last patient. The study demonstrated a statistically significant improvement in OS with a 23% risk reduction of death for RYDAPT plus standard chemotherapy over placebo plus standard chemotherapy (see Figure 2). Because survival curves plateaued before reaching the median, median survival could not be reliably estimated.

Figure 2 **Kaplan-Meier curve for overall survival, non-censored at the time of stem cell transplantation**

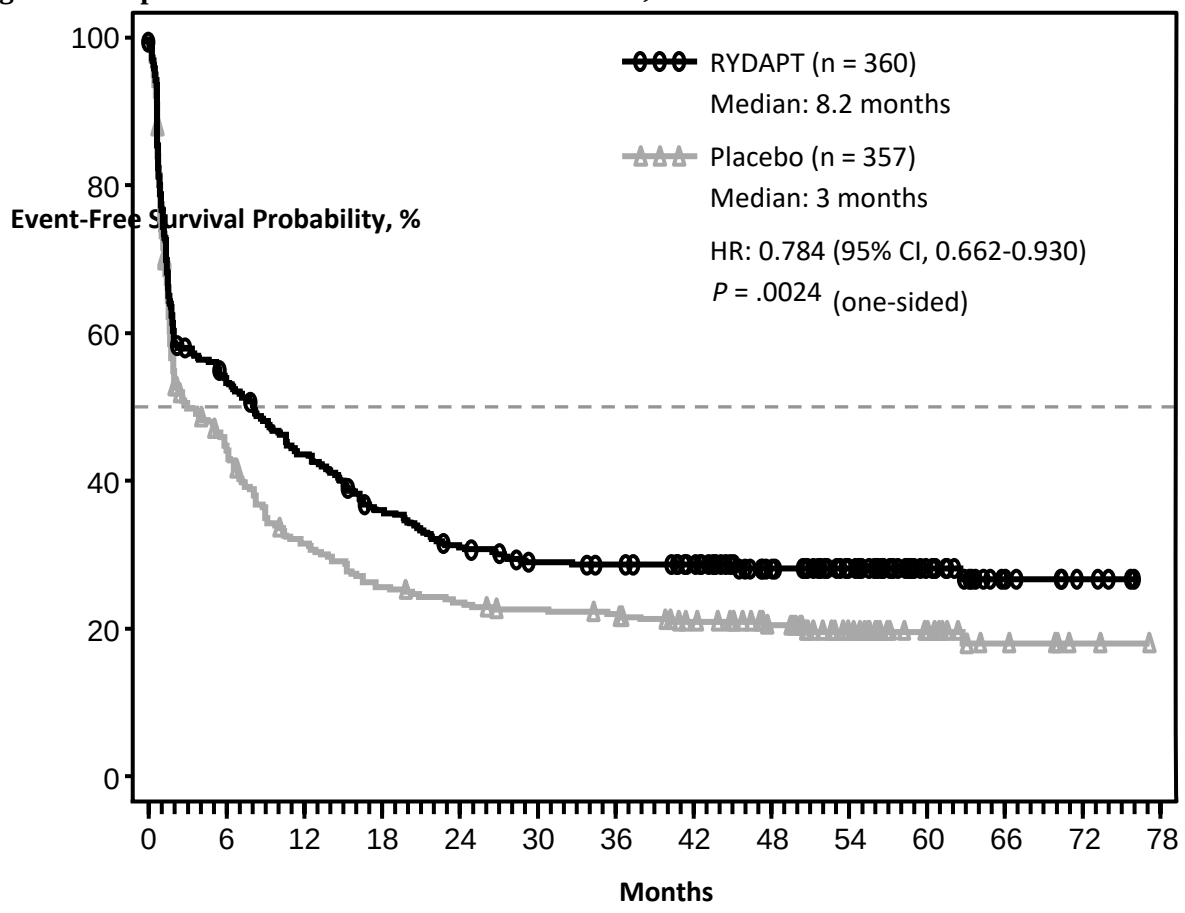


Patients at risk

Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**
Midostaurin	360	314	269	234	208	189	181	174	133	120	77	50	22	1	0
Placebo	357	284	221	179	163	152	148	141	110	95	71	45	20	1	0

The key secondary endpoint was event free survival (EFS; an event is defined as a failure to obtain a complete remission (CR) within 60 days of initiation of protocol therapy, or relapse, or death from any cause). The analysis of EFS showed a statistically significant improvement with a median of 8.2 months (95% CI: 5.4-10.7) for RYDAPT plus standard chemotherapy versus 3.0 months (95% CI: (1.9-5.9) for placebo plus standard chemotherapy with HR 0.78 (95% CI: 0.66, 0.93) and one-sided p-value of 0.0024.

Figure 3 - Kaplan-Meier curve for event-free survival, non-censored for SCT



Patients at risk

Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**
Midostaurin	360	190	153	124	106	95	92	83	65	51	27	9	4	0
Placebo	357	153	106	86	78	73	70	60	49	32	18	8	2	0

Secondary endpoint analyses for both OS [HR = 0.75 (95% CI: 0.54, 1.03); one-sided p=0.037] and EFS [HR = 0.81 (95% CI: 0.68, 0.98); one-sided p=0.012] when censored at the time of SCT also supported the clinical benefit with RYDAPT plus standard chemotherapy over placebo. There was a trend favoring RYDAPT for CR rate by day 60 for the midostaurin arm (58.9% versus 53.5%; one-sided p = 0.073). Disease-free survival (DFS) was measured from the date of first CR to the date of relapse or death from any cause, whichever occurred first. Median DFS in patients with CR within 60 days of treatment start was 26.7 months (19.35, NE) in the midostaurin arm and 15.5 months (11.33, 23.46) in the placebo arm (HR=0.71; 95% CI: 0.55, 0.92; one-sided p=0.0051).

A subgroup analysis of OS by gender showed no apparent OS advantage in female (n = 398) treated with RYDAPT where the hazard ratio was 1.01 (95% CI: 0.76, 1.34); the hazard ratio for male (n=319) was 0.53 (95% CI: 0.39, 0.72). This gender effect was not observed on the secondary efficacy endpoints (EFS, DFS and CR rate).

Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL)

The efficacy of RYDAPT in patients with ASM, SM-AHN and MCL, collectively referred to as advanced systemic mastocytosis (SM), were evaluated in two open-label, single-arm, multicenter studies (142 patients in total).

The pivotal study was a multicenter, single-arm phase II study in 116 patients with advanced SM (Study CPKC412D2201). The study excluded patients with acute-stage or life-threatening AHN. RYDAPT was administered orally at 100 mg twice daily until disease progression or intolerable toxicity. Of the 116 patients enrolled, 89 were considered eligible for response assessment and constituted the primary efficacy population (PEP). Of these, 73 patients had ASM (57 with an AHN), and 16 patients had MCL (6 with an AHN). The median age in the PEP was 64 years (range: 25 to 82 years), 64% of patients were male, and nearly all patients (97%) were Caucasian. Approximately one-third (36%) received prior anti-neoplastic therapy for SM. At baseline in the PEP, 65% of the patients had >1 measurable C-finding. The KIT D816V mutation was detected in 82% of patients.

The primary endpoint was overall response rate (ORR). Response rates were assessed based on the modified Valent and Cheson criteria and responses were adjudicated by a study steering committee. Secondary endpoints included duration of response. Responses to RYDAPT are shown in Table 8. Activity was observed regardless of number of prior therapies, and presence or absence of an AHN. Confirmed major or partial responses occurred in 46 of 73 patients with a documented KIT D816V mutation, 7 of 16 with wild-type or unknown status with respect to KIT D816V mutation, and 21 of 32 having prior therapy for SM. Forty-six percent of patients had a decrease in bone marrow infiltration exceeded 50% and 58% had a decrease in serum tryptase levels exceeded 50%. Spleen volume decreased by ≥10% in 68.9% of patients with at least 1 post-baseline assessment (26.7% of patients had a reduction of ≥35%, which correlates with a 50% decrease by palpation).

The median time to response was 0.3 months (range: 0.1 to 3.7 months). The median duration of follow-up was 43 months.

Table 8 - Efficacy of RYDAPT in ASM, SM-AHN and MCL: Primary efficacy population

	All N=89	**ASM patients N=16**	**SM-AHN patients N=57**	**MCL patients N=16**
Primary Endpoint				
Overall Response, n (%)	53 (59.6)	12 (75.0)	33 (57.9)	8 (50.0)
(95% CI)	(48.6, 69.8)	(47.6, 92.7)	(44.1, 70.9)	(24.7, 75.3)
Major Response, n (%)	40 (44.9)	10 (62.5)	23 (40.4)	7 (43.8)
Partial Response, n (%)	13 (14.6)	2 (12.5)	10 (17.5)	1 (6.3)
Stable Disease, n (%)	11 (12.4)	1 (6.3)	7 (12.3)	3 (18.8)

Progressive Disease, n (%)	10 (11.2)	1 (6.3)	6 (10.5)	3 (18.8)
Secondary Endpoint				
Median Duration of Response, months (95% CI)	31.4 (10.8; NE)	NR (24.1, NE)	12.7 (7.4, 31.4)	NR (3.6, NE)

NE: Not Estimated; NR: Not Reached

As a post-hoc exploratory analysis, efficacy was also assessed per the 2013 International Working Group - Myeloproliferative Neoplasms Research and Treatment - European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus criteria. Response of RYDAPT was determined using a computational algorithm. There were 115 patients evaluable for response assessment, of whom 47 (41%) had prior therapy for SM, and 93 (81%) had a documented D816V mutation at baseline. All responses were considered and required a 12-week confirmation. Table 9 provides the results of this analysis.

Table 9 - Efficacy of RYDAPT in ASM, SM-AHN and MCL per IWG MRT ECNM consensus criteria using an algorithmic approach

	All patients evaluated	**ASM**	**SM-AHN**	**MCL**	**Subtype unknown**
	N=115	**N=16**	**N=72**	**N=21**	**N=6**
Overall response* rate, n (%)	43 (37.4)	10 (62.5)	23 (31.9)	7 (33.3)	3 (50.0)
(95% CI)	(28.5, 46.9)	(35.4, 84.8)	(21.4, 44.0)	(14.6, 57.0)	(11.8, 88.2)
Best overall response, n (%)					
Complete remission	2 (1.7)	1 (6.3)	0	1 (4.8)	0
Partial remission	19 (16.5)	5 (31.3)	9 (12.5)	3 (14.3)	2 (33.3)
Clinical improvement	22 (19.1)	4 (25.0)	14 (19.4)	3 (14.3)	1 (16.7)
Duration of response					
n/N (%)	6/43 (14.0)	1/10 (10.0)	5/23 (21.7)	0/7 (0.0)	0/3 (0.0)
median (95% CI)	NE	NE (10.3, NE)	NE (17.3, NE)	NE	NE
range	2.8+ - 60.5+	10.2+ - 36.4+	2.8+ - 51.8+	3.3+ - 55.9+	20.5+ - 60.5+

NE: Not Estimated

*Confirmation period for responses: 12 weeks. Analysis including ascites C-finding. Patients who received high-dose corticosteroids were considered evaluable for response.+ indicates a censored value

The supportive study was a single arm, multicenter, open-label phase II study of 26 patients with advanced SM (CPKC412A2213). RYDAPT was administered orally at 100 mg twice daily. Lack of a major response (MR) or partial response (PR) by the end of the second cycle required in

discontinuation from the study treatment. Twenty (76.9%) patients had ASM (17 [85%] with AHN) and 6 patients (23.1%) had MCL (2 [33.3%] with AHN). The median age was 64.5 years with half of the patients ≥65 years. At baseline, 88.5% had >1 C-finding and 69.2% had received at least one prior anti-neoplastic regimen.

The primary endpoint was ORR evaluated by the Valent criteria during the first two cycles of treatment. Nineteen patients (73.1%; 95% CI = [52.2, 88.4]) achieved a response during the first two cycles of treatment (13 MR; 6 PR) per investigator assessment. Patients who received concomitant corticosteroids were included. The median duration of follow-up was 73 months, and the median duration of response has not been reached.

DETAILED PHARMACOLOGY

Safety pharmacology studies indicate that midostaurin is unlikely to interfere with vital functions of the central nervous systems. In the repeat dose studies in dogs, a decrease in heart rate and a prolongation of the P-Q interval was seen in individual animals at 10 and 30 mg/kg; there were no morphological changes in the heart.

TOXICOLOGY

Midostaurin has been evaluated in single/repeated dose toxicity, genotoxicity, reproductive and developmental toxicity studies.

In the repeat dose studies, the key target organs identified were the gastrointestinal tract (emesis in dogs and monkeys, diarrhea and mucosal alteration), testes (decreased spermatogenesis), bone marrow (hypocellularity), heart (prolongation of the P-Q interval) and lymphoid organs (depletion/atrophy). The effect on the bone marrow and lymphoid organs was accompanied by hematological changes of decreased WBCs, lymphocytes and erythrocytic parameters. An increase in liver enzymes (ALT and AST) was seen consistently in rats, and in dogs and monkeys in long term studies of >3 months duration. There were no corresponding pathological changes in the liver. Inhibition of spermatogenesis was seen in dogs at doses >3 mg/kg. The no-adverse-effect level after 12 months of treatment was 1 mg/kg in dogs and 3 mg/kg in rats, although the systemic exposure was much larger in humans.

Fertility, Reproductive and Developmental Toxicity

Oral administration of midostaurin at 10, 30 and 60 mg/kg/day was associated with reproductive toxicity in male and female rats at doses ≥10 mg/kg/day. In males, testicular degeneration and atrophy was observed at doses ≥10 mg/kg/day and alterations in sperm motility, a decrease in sperm counts, and a decrease in reproductive organ weights were observed at 60 mg/kg/day. In females, increased resorptions, decreased pregnancy rate, number of implants and live embryos were observed at 60 mg/kg/day. Inhibition of spermatogenesis was seen in dogs at doses ≥3 mg/kg/day. The concentrations in rats at 10 mg/kg/day and dogs at 3 mg/kg/day are 100-fold below the human therapeutic exposures at the recommended dose of 50 mg twice daily based on AUC.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of midostaurin at 3, 10, and 30 mg/kg/day and at 2, 10 and 20 mg/kg/day, respectively, during the period of organogenesis. An increase in number of late resorptions was observed at all dose levels and a reduction in fetal weight and skeletal ossification was observed in rats at the high dose of 30 mg/kg/day; no maternal toxicity was observed. In rabbits, maternal toxicity was observed at all dose levels. Mortality in dams, reduced fetal weight and delayed ossification was observed at 10 and 20 mg/kg/day. The concentrations at which maternal and fetal toxicity occurred in both species are over 50-fold below the human therapeutic exposures at the recommended dose of 50 mg twice daily based on AUC comparisons across species.

In a pre- and post-natal developmental study, rats were given oral doses of 5, 15, and 30 mg/kg/day during gestation through lactation up to weaning. Maternal toxicity including signs of dystocia and reduced litter size were observed at 30 mg/kg/day. Lower body weights, a decrease in the mean day of development for eye opening and an increase in the mean day of development for auricular startle were noted in the rat pups (F1 generation) exposed to midostaurin at 30 mg/kg/day. Maternal systemic exposure at 30 mg/kg (based on AUC) was approximately 17-fold below the human therapeutic exposures at the recommended dose of 50 mg twice daily.

Juvenile animal studies

In a toxicity study in juvenile rats, midostaurin was administered at 2, 5 and 15 mg/kg/day from days 7 to 70 postpartum. A reduction in body weight, hemorrhage, mixed cell infiltration in the lungs and erythrocytosis/erythrophagocytosis in the mesenteric lymph nodes were seen at 15 mg/kg/day. There were no effects on physical development, sensory function, behavioral or reproductive function. The no-observed-adverse-effect level was 5 mg/kg/day.

Genotoxicity

In vitro and *in vivo* genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of mutagenic or clastogenic activity.

Carcinogenesis

No carcinogenicity studies have been performed with midostaurin.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrRYDAPT®

Midostaurin capsules

Read this carefully before you start taking **RYDAPT®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RYDAPT**.

What is RYDAPT used for?

RYDAPT is used in combination with other chemotherapy treatments to treat acute myeloid leukemia (AML) in adults who have a new diagnosis of a defect in a gene called FLT3. A test will confirm if you have the FLT3 kind of AML. AML is a type of cancer of white blood cells.

RYDAPT is also used on its own in adults to treat diseases called aggressive systemic mastocystosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL). These are disorders in which the body produces too many mast cells, a type of white blood cell. Symptoms are caused when too many mast cells infiltrate organs like the liver, bone marrow and spleen, or release substances like histamine into the blood.

How does RYDAPT work?

Midostaurin blocks the action of some enzymes (kinases) of cells that are not normal. This stops their division and growth.

What are the ingredients in RYDAPT?

Medicinal ingredients: midostaurin (from a benzyl alcohol and ethanol solvate form of midostaurin).

Non-medicinal ingredients: all-rac-α-tocopherol (vitamin E), corn oil mono-di-triglycerides, ethanol anhydrous, gelatin, glycerol, iron oxide red, iron oxide yellow, macrogol 400, macrogolglycerol hydroxystearate, purified water, red pharmaceutical ink, titanium dioxide.

RYDAPT comes in the following dosage forms:

Capsules, 25 mg

Do not use RYDAPT if:

- You are allergic to midostaurin or any of the other ingredients of RYDAPT.
- You are under 18 years old.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RYDAPT. Talk about any health conditions or problems you may have, including if you:

- have any infections.
- have heart disorders.
- have problems with your lungs or problems breathing.

Other warnings you should know about:

Breast-feeding, pregnancy, females of child-bearing potential and male patients
Tell your doctor if you:
- are breast-feeding.
- are pregnant.
- think you might be pregnant.
- are planning to have a baby.

Your doctor will talk to you about the risks of taking RYDAPT if you are breast-feeding or pregnant. Breast-feeding should be stopped during treatment and for at least 4 months after stopping RYDAPT.

Do not take RYDAPT if you are pregnant. RYDAPT may harm your unborn baby. If you could get pregnant, take a pregnancy test 7 days before taking RYDAPT. You must use effective birth control while you are taking RYDAPT and for 4 months after you stop taking it. It is not known if RYDAPT will reduce the effectiveness of hormonal contraceptives. If you are on hormonal contraceptives, such as the pill, you should add a barrier method of birth control to be sure to prevent pregnancy, such as a condom. Ask your doctor about options of effective birth control.

Male patients should use condoms during sex during treatment and for 4 months after stopping RYDAPT.

Fertility problems

RYDAPT may impair fertility in men and women. It is unknown whether these effects are reversible. You should discuss this with your doctor before starting treatment.

RYDAPT can interact with many drugs. This includes over the counter and herbal drugs. Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RYDAPT:
- some medicines used to treat infections, such as ketoconazole or clarithromycin,
- some medicines used to treat epilepsy, such as carbamazepine,
- medicines used to treat tuberculosis, such as rifampicin,
- some medicines used to treat depression such as the herbal medicine St. John's Wort. It is also known as hypericum perforatum,
- medicines used to treat HIV, such as ritonavir,
- medicines that may cause a heart rhythm disorder called prolongation of the QT interval.

If you are taking any of these, your doctor might prescribe other alternative medicines.

If you are already taking RYDAPT, tell your doctor if you are prescribed a new drug.

Do not eat or drink anything that contains grapefruit while taking RYDAPT.

How to take RYDAPT:

RYDAPT should only be started by a physician experienced in anti-cancer drugs.

Take RYDAPT exactly as your doctor or pharmacist has told you. Check with them if you are not sure. Do NOT exceed or stop taking the dose unless your doctor tells you to. Stopping your treatment with RYDAPT may cause your condition to become worse. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

Take RYDAPT:
- by mouth.
- whole with a glass of water. Do NOT open, crush or chew.
- twice a day at about 12 hour intervals. For example take it at breakfast and dinner time.
- with food to help to prevent nausea.

Your doctor will give you medications to help prevent the nausea and vomiting during treatment with RYDAPT.

Recommended dose:

Patients with AML:
On days 8 to 21 of each cycle, take 50 mg (2 capsules) twice a day. This is a total of 4 capsules per day.

The doctor will decide how long each cycle will last.

Patients with ASM, SM-AHN, or MCL:
Take 100 mg (4 capsules) twice a day. This is a total of 8 capsules per day.

Depending on how you react to RYDAPT, your doctor may adjust your treatment. Your doctor may also stop your treatment for a period of time or entirely.

Overdose:

If you think you have taken too much RYDAPT, or if someone else accidentally takes your medicine, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. Show the pack of RYDAPT. Medical treatment may be necessary.

Missed Dose:

If you miss a dose, skip the missed dose and continue as usual. Do not take a double dose to make up for forgotten capsules. Instead, wait until it is time for your next dose.

If vomiting occurs you should not take an additional dose of RYDAPT, but should take the next usual prescribed dose.

What are possible side effects from using RYDAPT?

These are not all the possible side effects you may feel when taking RYDAPT. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Red or purple, flat, pinhead spots under the skin. They are called petechiae.
- Dry skin
- Excessive sweating, which is called hyperhidrosis.
- Swelling of the eyelid. It is called eyelid edema
- Eye pain, blurred vision, abnormal intolerance to light. This is called keratitis.
- Problem to fall asleep. This is called insomnia
- Throat pain, which is called laryngeal pain and mouth-throat pain, which is called oropharyngeal pain
- Sore throat combined with runny nose. This is called nasopharyngitis.
- Involuntary shaking of the body, which is called a tremor
- Headache
- Dizziness including dizziness with spinning sensation which is called vertigo
- Disturbance in attention
- Upper abdominal pain
- Diarrhea
- Constipation
- Upset stomach, indigestion. This is called dyspepsia.
- Pain in back, joints, neck, bones and arm and legs
- Cold sores in the mouth due to viral infection. This is called oral herpes.
- Feeling of pressure or pain in the cheeks and forehead. This is called sinusitis.
- Generalized swelling. This is called edema.
- Swelling of the lower limbs (calves, ankles). This is called edema peripheral.
- Tiredness. This is called fatigue.
- Weakness. This is called asthenia.
- Chills
- Bruise. This is called hematoma or contusion.
- Fall.

During RYDAPT treatment, you may also have side effects of abnormal blood test results (very common), which can give your doctor information on the functioning of some parts of your body, for example:

- High levels of the following enzymes:
    - Enzymes related to liver

Your heart and lung function will also be checked regularly.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Allergic Reaction: difficulty breathing or swallowing, dizziness, swelling of the face, lips, tongue or throat, severe itching, with a red rash or raised bumps			X
Decreased Blood Clotting		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Activity: spontaneous bleeding or bruising			
Lymphopenia/Neutropenia: weakness, fever, sore throat or mouth ulcers due to infections		X	
Infection at catheter site: redness of the skin, pain, tenderness, swelling at the site of the flexible tube	X		
Dermatitis exfoliative: skin rash with flaking or peeling	X		
Epistaxis: nose bleeding	X		
Dyspnea: shortness of breath, labored breathing	X		
Hypotension: dizziness, light headedness	X		
Stomatitis: mouth sores	X		
Nausea	X		
Vomiting	X		
Pyrexia: fever	X		
Low level of potassium in the blood (hypokalemia): irregular heartbeats, muscle weakness and spasm, generally feeling unwell.	X		
Increased blood sugar (hyperglycemia)**:** frequent hunger, frequent thirst, increased volume of urination.	X		
High level of sodium in the blood (hypernatremia): thirst, weakness, cramps, headaches, confusion, convulsions, impaired consciousness	X		
Pleural effusion (fluid collection on the lungs/chest cavity): chest pain, difficult or painful breathing, cough		X	
Hemorrhoids: itching, irritation or pain around the anus, painful bowel movements	X		
Upper respiratory tract infection: cough, sore throat, stuffy or runny nose, sneezing	X		
Urinary tract infection or cystitis: painful and frequent		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
urination due to a urinary bladder inflammation			
COMMON			
High level of uric acid in the blood (hyperuricemia): repeated pain to the side and the abdomen which may spread to your groin area	X		
High level of calcium in the blood (hypercalcemia): periodic pain in upper right abdomen (accompanied by nausea and vomiting), repeated pain to the side and the abdomen which may spread to your groin area , bone pain, nausea, vomiting, constipation, stomach pain, frequent urination, thirst, and muscle weakness	X		
Acute Respiratory Distress Syndrome: Severe shortness of breath, labored and unusually rapid breathing, low blood pressure, confusion and extreme tiredness		X	
Blood clot in catheter (flexible tube)		X	
Weight increased	X		
Hypertension: headache, dizziness	X		
Fainting		X	
Anorectal discomfort	X		
Sinus tachycardia: fast heart beat	X		
Pericardial effusion (fluid collection in the sac around the heart): chest pain that feels better when you sit up rather than lie down. Feel light-headed or pass out. Irregular, fast, or forceful heartbeat. Difficult or painful breathing, cough		X	
Pneumonia: fever, cough, difficult or painful breathing, wheezing, chest in pain when breathing		X	
Gastrointestinal hemorrhage: vomiting of blood, black or bloody stools		X	
Erysipelas: red, swollen painful	X		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
rash on any part of the skin			
Bronchitis: cough with phlegm, chest pain, and fever	X		
Shingles: pain, burning, numbness or tingling, rash, fluid-filled blisters		X	
UNCOMMON			
Sepsis or Neutropenic Sepsis: Infections, fever, low blood pressure, decreased urination, rapid pulse, rapid breathing		X	
UNKNOWN FREQUENCY			
Infections or Lung Problems: new or worsening fever, cough with or without mucous, chest pain, trouble breathing or shortness of breath.			X
Heart Problems: chest pain or discomfort. Lightheadedness, fainting, dizziness. Blue colour of your lips, fingers or toes. Shortness of breath. Swelling of your legs of feet.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Do not store above 30°C. Store in the original package to protect from moisture.
- Keep out of reach and sight of children.
- Do not take this medicine after the expiry date, which is stated on the box.

Ask your pharmacist how to dispose of medicines you no longer use.

If you want more information about RYDAPT:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.novartis.ca), or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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