For the treatment of adults with newly diagnosed FLT3+ AML eligible for intensive chemotherapy

READY FOR RYDAPT IN AML

A GUIDE TO MANAGING THE TREATMENT OF APPROPRIATE PATIENTS WITH FLT3+ AML

In addition to the adverse reactions in this brochure, there are other adverse reactions and laboratory abnormalities associated with RYDAPT treatment. Please consult the Summary of Product Characteristics for further guidance.

INDICATION

RYDAPT is indicated in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by RYDAPT single-agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive.

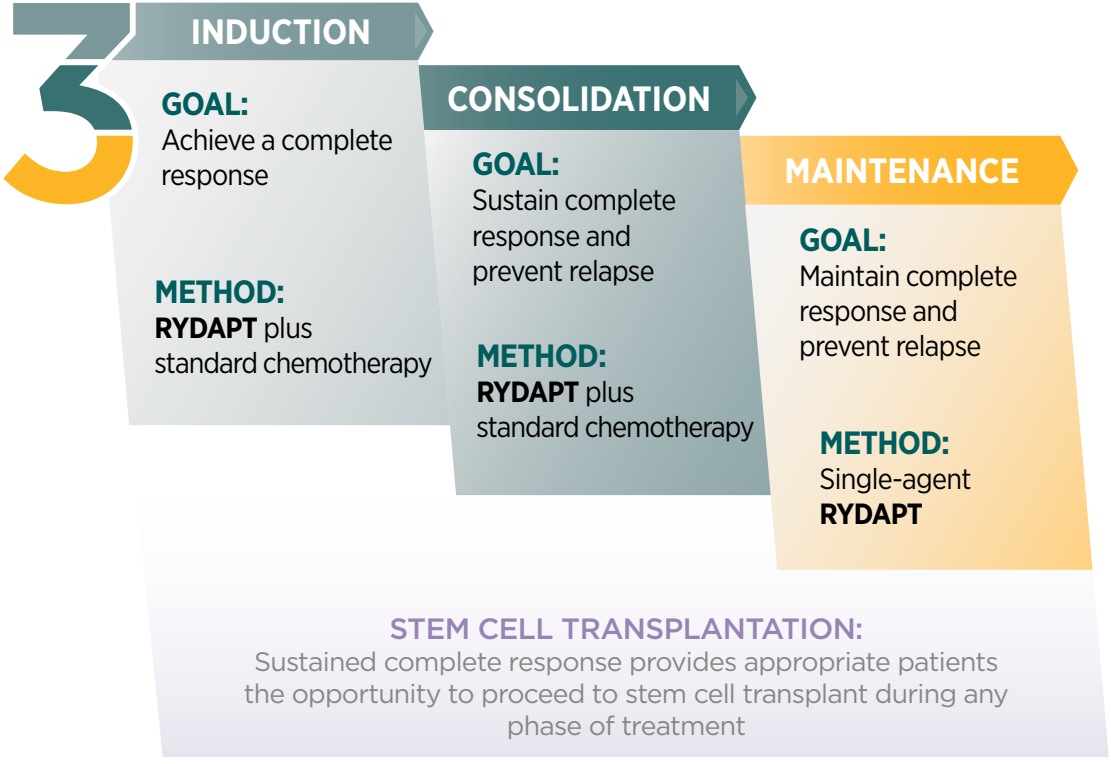
Important prescribing and safety information is available on pages 12-15.

RYDAPT® midostaurin

For the treatment of patients with newly diagnosed FLT3+ AML eligible for intensive chemotherapy

THE FIRST AGENT APPROVED IN 3 PHASES OF TREATMENT IN NEWLY DIAGNOSED FLT3+ AML

RYDAPT was studied throughout the 3 phases of treatment to help adults with newly diagnosed FLT3+ AML extend survival[1,2]



- The European LeukemiaNet 2017 recommendations advise *FLT3* testing* at diagnosis and obtaining results within 3 days[3]

RYDAPT helps your adult patients with newly diagnosed FLT3+ AML achieve their treatment goals[1]

**FLT3* mutation testing is performed by the Laboratory of Personalized Molecular Medicine GmbH (Germany), a subsidiary of Invivoscribe Technologies, Inc.

IMPORTANT DOSING AND ADMINISTRATION INFORMATION[1]

Recommended dosing regimen throughout the course of treatment

not actual size

The recommended dose of RYDAPT is 50 mg orally twice daily.

RYDAPT should be taken orally twice daily at approximately 12-hour intervals.

RYDAPT is dosed on days 8 to 21 of induction and consolidation chemotherapy cycles, and then for patients in complete response every day as single-agent maintenance therapy until relapse for up to 12 cycles of 28 days each.

RYDAPT capsules should be swallowed whole with a glass of water. RYDAPT should be taken with food.

RYDAPT is dispensed in packs containing 112 (4 packs of 28) soft capsules. Capsules should not be used after the expiry date (= EXP) printed on the pack.

INDUCTION CHEMOTHERAPY[1,2] (1-2 cycles, 21 days per cycle)	CONSOLIDATION CHEMOTHERAPY[1,2] (up to 4 cycles, 21 days per cycle)	SINGLE-AGENT MAINTENANCE THERAPY (up to 12 cycles, 28 days per cycle)
RYDAPT 50 mg twice daily on days 8-21	**RYDAPT** 50 mg twice daily on days 8-21	**RYDAPT** 50 mg twice daily on days 1-28

- If a dose is missed, the patient should take the next dose at the scheduled time
- Prophylactic antiemetics should be administered in accordance with local medical practice as per patient tolerance
- If vomiting occurs during treatment, the patient should not take an additional dose before taking the next scheduled dose
- Consult the prescribing information for dose modification recommendations

Important prescribing and safety information is available on pages 12-15.

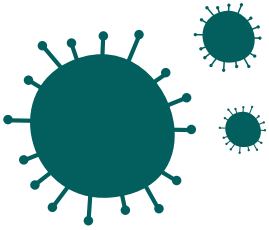
RYDAPT® midostaurin

MONITOR FOR AND MANAGE INFECTIONS DURING THERAPY

INCIDENCE OF DEVICE-RELATED INFECTION

(All Grades)	(Grades 3/4)
24% with RYDAPT	**15.7%** with RYDAPT

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. If a diagnosis of infection is made, appropriate treatment must be instituted promptly, including, as needed, the discontinuation of RYDAPT.

Caution is required when co-administering midostaurin with strong CYP3A4 inhibitors including, but not limited to, antifungals (eg, ketoconazole), certain antivirals (eg, ritonavir), macrolide antibiotics (eg, clarithromycin), and nefazodone.

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 midostaurin-related toxicity.

Important prescribing and safety information is available on pages 12-15.

MONITOR FOR AND MANAGE NEUTROPENIA DURING THERAPY

INCIDENCE OF FEBRILE NEUTROPENIA

(All Grades)

83.4%

with RYDAPT

(Grades 3/4)

83.5%

with RYDAPT

INCIDENCE OF DECREASED ABSOLUTE NEUTROPHIL COUNT (ANC)

(All Grades)

86.7%

with RYDAPT

(Grades 3/4)

85.8%

with RYDAPT

During maintenance therapy:

Grade 4 neutropenia (ANC <0.5 x 10^9/L)

Interrupt RYDAPT until ANC ≥1.0 x 10^9/L, then resume RYDAPT at 50 mg twice daily

If neutropenia (ANC <1.0 x 10^9/L) persists >2 weeks and is suspected to be related to RYDAPT, discontinue RYDAPT

Neutropenia has occurred in patients receiving RYDAPT as monotherapy and in combination with chemotherapy.

In patients who develop unexplained severe neutropenia, treatment with RYDAPT should be interrupted as recommended.

- RYDAPT should be discontinued in patients who develop recurrent or prolonged severe neutropenia that is suspected to be related to RYDAPT

Warnings and precautions include neutropenia and infections, cardiac dysfunction, pulmonary toxicity, embryo-fetal toxicity and lactation, severe hepatic impairment, severe renal impairment, interactions, and excipients. Please see the full safety information on pages 12-15.

RYDAPT® midostaurin

MONITOR FOR NAUSEA AND VOMITING DURING THERAPY[1]

INCIDENCE OF NAUSEA

(All Grades)

83.4%

with RYDAPT

(Grades 3/4)

5.8%

with RYDAPT

INCIDENCE OF VOMITING

(All Grades)

60.7%

with RYDAPT

(Grades 3/4)

2.9%

with RYDAPT

Lower incidence of nausea and vomiting (all grades) occurred with RYDAPT during the maintenance phase

Nausea: **46.4% vs 17.9% with placebo**

Vomiting: **19% vs 5.4% with placebo**

Important prescribing and safety information is available on pages 12-15.

MANAGING NAUSEA AND VOMITING[1]

RYDAPT should be taken with food.

Prophylactic antiemetics should be administered in accordance with local medical practice as per patient tolerance.

If vomiting occurs during treatment, the patient should not take an additional dose before taking the next scheduled dose.

Please consider the following dose modifications.

For grade 3/4 pulmonary infiltrates: Interrupt RYDAPT therapy for the remainder of any given treatment cycle. Resume RYDAPT at the same dose when infiltrate resolves to Grade ≤1.

For grade 3/4 non-haematological toxicities: Interrupt treatment until toxicities possibly related to RYDAPT have resolved to grade ≤2, and then resume treatment.

References: 1. RYDAPT [Summary of Product Characteristics]. Novartis Pharma AG; 2017. **2.** Data on file. Study no. CPKC412A2301. Novartis Pharmaceuticals Corp; 2016. **3.** Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.

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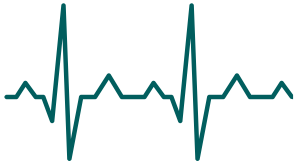
MANAGING QTc PROLONGATION[1]



Effect of RYDAPT on QTc prolongation
An increased frequency of QTc prolongation was noted in patients treated with RYDAPT, but a mechanistic explanation for this observation was not found. Caution is warranted in patients at risk of QTc prolongation (eg, due to concomitant medicinal products and/or electrolyte disturbances). Interval assessments of QT by electrocardiogram should be considered if RYDAPT is taken concurrently with medicinal products that can prolong QT interval.

QTc interval >470 msec and ≤500 msec
Decrease RYDAPT to 50 mg once daily for the remainder of the cycle. Resume RYDAPT at the initial dose in the next cycle provided that QTc interval improves to ≤470 msec at the start of that cycle. Otherwise, continue RYDAPT 50 mg once daily.

QTc interval >500 msec
Withhold or interrupt RYDAPT for the remainder of the cycle. If QTc improves to ≤470 msec just prior to the next cycle, resume RYDAPT at the initial dose. If QTc interval is not improved in time to start the next cycle, do not administer RYDAPT during that cycle. RYDAPT may be held for as many cycles as necessary until QTc improves.

Important prescribing and safety information is available on pages 12-15.

MANAGING DRUG-DRUG INTERACTIONS[1]

Effect of other drugs on RYDAPT
Medicinal products or substances known to affect the activity of CYP3A4 may affect the plasma concentrations of midostaurin and therefore the safety and/or efficacy of RYDAPT.

Strong CYP3A4 Inducers
Strong CYP3A4 inducers decrease exposure of RYDAPT and its active metabolites. Concomitant use of RYDAPT with strong inducers of CYP3A4 (eg, carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort [Hypericum perforatum]) is contraindicated. Please see the RYDAPT Summary of Product Characteristics for more information on RYDAPT and strong CYP3A4 inducers.

Strong CYP3A4 inhibitors
Strong CYP3A4 inhibitors may increase midostaurin blood concentrations. Caution is required when co-administering midostaurin with strong CYP3A4 inhibitors including, but not limited to, antifungals (eg, **ketoconazole**), certain antivirals (eg, **ritonavir**), macrolide antibiotics (eg, **clarithromycin**), and **nefazodone**. 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 midostaurin-related toxicity.

Effect of RYDAPT on other drugs
Based on in vitro results regarding the inhibition or induction of CYP enzymes and/or transporter systems by midostaurin, medicinal products with a narrow therapeutic range that are substrates of these enzymes and/or transporter systems should be used with caution when co-administered with midostaurin. Dose adjustment may be required to maintain optimal exposure.

RYDAPT® midostaurin

MANAGING RYDAPT TREATMENT IN SPECIAL POPULATIONS[1]

Patients with renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment. Caution is warranted in patients with severe renal impairment, and patients should be monitored for toxicity.

Patients with hepatic impairment
No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. Caution is warranted in patients with severe hepatic impairment, and patients should be monitored for toxicity.

The recommended dose of RYDAPT is **50 mg twice daily**

Important prescribing and safety information is available on pages 12-15.

Elderly patients (≥65 years)
No dose adjustment is required in patients >65 years of age.

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.

Pregnant and breastfeeding women
RYDAPT is not recommended during pregnancy. RYDAPT can cause foetal harm when administered to pregnant women. Pregnant women should be advised of the potential risk to the foetus.

Breastfeeding should be discontinued during treatment with RYDAPT and for at least 4 months after stopping treatment.

Women of childbearing potential and contraceptive measures
Women of childbearing potential should be informed that midostaurin may be harmful to the developing foetus. RYDAPT is not recommended in women of childbearing potential not using contraception. Sexually active women of childbearing potential should take a pregnancy test before starting treatment with RYDAPT and use effective contraception (methods that result in <1% pregnancy rates) when using RYDAPT and for at least 4 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception.

RYDAPT® midostaurin

BASIC SUCCINCT STATEMENT FOR RYDAPT (midostaurin) CAPSULES

Important note: Before prescribing, consult full prescribing information of RYDAPT.

Presentation: Soft capsules containing 25 mg of midostaurin.

Indications: Rydapt® is indicated

- in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by single agent maintenance therapy, for patients with newly diagnosed FLT3 mutation-positive acute myeloid leukemia (AML)

Dosage and administration:

AML Adults: Recommended dose is 50 mg twice daily. Rydapt is dosed on days 8 to 21 of induction and consolidation chemotherapy, and then for patients in complete response twice daily as a single agent maintenance for 12 cycles of 28 days each.

Dose modifications: Management of adverse drug reactions (ADRs) may require treatment interruption, dose reduction or treatment discontinuation.

Special populations:

- *Renal impairment:* Mild or moderate: no dose adjustment required. Severe or end stage renal disease: No data
- *Hepatic impairment:* Mild or moderate: no dose adjustment required. Severe: No data
- *Geriatrics (≥65 years):* No dose adjustment required. 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
- *Pediatrics:* Safety and efficacy have not been established

Contraindications: Patients with hypersensitivity to midostaurin or to any of the excipients. Concomitant administration of potent CYP3A4 inducers.

Warnings and precautions:

- **Neutropenia and infections:** Rydapt can cause severe neutropenia. Consider treatment interruption. Monitor White Blood Cell counts regularly and especially at treatment initiation. Delay starting therapy with Rydapt until active serious infections have resolved. Observe and promptly manage symptoms of serious infection in patients receiving Rydapt
- **Cardiac dysfunction:** Transient decreases in Left Ventricular Ejection Fraction and Congestive Heart Failure were observed in patients treated with Rydapt in Advanced SM studies. Use Rydapt with caution in patients at risk and monitor patients by assessing LVEF when clinically indicated (at baseline and during treatment). An increased frequency of QTc prolongation was observed in Rydapt-treated patients, without an identified mechanistic explanation. Use Rydapt with caution in patients at risk and consider interval QT assessment by ECG when taken concurrently with medicines that can prolong QT interval
- **Pulmonary toxicity:** Interstitial Lung Disease (ILD) and pneumonitis have been reported during treatment with Rydapt. Monitor patients for severe pulmonary symptoms of ILD or pneumonitis and discontinue Rydapt if patients experience Grade 3 symptoms
- **Embryo-fetal toxicity and lactation:** Rydapt can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use contraception during treatment and for at least 4 months after stopping treatment with Rydapt. Women using hormonal contraceptives should add a barrier method. Advise nursing women to discontinue breastfeeding during treatment and for at least 4 months after stopping treatment with Rydapt
- **Severe hepatic impairment:** Caution is warranted in patients with severe hepatic impairment and patients should be monitored for toxicity
- **Severe renal impairment:** Caution is warranted in patients with severe renal impairment and patients should be monitored for toxicity
- **Interactions:** Caution is required when concomitantly prescribing with strong inhibitors of CYP3A4
- **Excipients:** Rydapt contains macrogolglycerol hydroxystearate, which may cause stomach discomfort and diarrhoea. Rydapt contains ethanol anhydrous which may be harmful in patients with alcohol related problems, epilepsy or liver problems or during pregnancy or breast feeding

RYDAPT® midostaurin

BASIC SUCCINCT STATEMENT FOR RYDAPT (midostaurin) CAPSULES (cont'd)

Pregnancy, lactation, females of reproductive potential:

Pregnancy: Rydapt can cause fetal harm. Pregnant women should be advised of the potential risk. Rydapt is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation: Breast-feeding should be discontinued during treatment with Rydapt and for at least 4 months after stopping treatment.

Females and males of reproductive potential:

- **Pregnancy testing:** A pregnancy test is recommended prior to starting treatment
- **Contraception:** Sexually active females of reproductive potential should use effective contraception during treatment with Rydapt and for at least 4 months after stopping treatment

Infertility: May impair fertility.

Adverse drug reactions:
AML:

Very common (≥10%): Device related infections, febrile neutropenia, petechiae, lymphopenia, hypersensitivity, insomnia, headache, hypotension, epistaxis, laryngeal pain, dyspnoea, nausea, vomiting, stomatitis, abdominal pain upper, haemorrhoids, hyperhidrosis, exfoliative dermatitis, back pain, arthralgia, pyrexia, hyperglycaemia, activated partial thromboplastin time prolonged, absolute neutrophils decreased, haemoglobin decreased, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, hypokalaemia, hypernatraemia.

Common (1 to 10%): Upper respiratory tract infection, hyperuricaemia, syncope, tremor, eyelid oedema, hypertension, sinus tachycardia, pericardial effusion, nasopharyngitis, pleural effusion, acute respiratory distress syndrome, anorectal discomfort, abdominal discomfort, dry skin, keratitis, neck pain, bone pain, pain in extremities, catheter-related thrombosis, weight increased, hypercalcaemia.

Uncommon (0.1 to 1%): Neutropenic sepsis.

Interactions:

- Caution when co-administration of strong CYP3A4 inhibitors including, but not limited to, ketoconazole, ritonavir, clarithromycin and nefazodone as strong CYP3A4 inhibitors may significantly increase exposure to midostaurin. Consider alternative therapeutic agent or monitor patient closely for toxicity. Clinical relevance limited
- Co-administration of strong CYP3A4 inducers including, but not limited to carbamazepine, rifampin or St. John's Wort may significantly decrease exposure to midostaurin. Concomitant use of Rydapt with strong CYP3A4 inducers is contraindicated
- The PK of midazolam (sensitive CYP34A substrate) was not affected following three dosing days of midostaurin in healthy subjects
- Medicinal products with a narrow therapeutic range that are substrates of CYP3A4/5, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, P-gp, BCRP or OATP1B1 should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure

Packs and prices: Country-specific.

Legal classification: Country-specific.

READY FOR RYDAPT

When treating adults with newly diagnosed FLT3+ AML eligible for intensive chemotherapy[1]:

RYDAPT is indicated for 3 phases of treatment
- Induction, consolidation, and maintenance. Please see page 2

not actual size

Dosing and administration
- The recommended dose of RYDAPT is 50 mg taken orally twice daily at around 12-hour intervals with a whole glass of water and food. Please see page 3

Infections
- Patients should be monitored for signs and symptoms of infection and, if a diagnosis of infection is made, appropriate treatment should be instituted promptly. Please see page 4

Neutropenia
- Neutropenia has occurred in patients receiving RYDAPT as monotherapy and in combination with chemotherapy. Please see page 5

Nausea and vomiting
- If vomiting occurs during treatment, the patient should not take an additional dose before taking the next scheduled dose. Please see pages 6-7

Special populations
- Help manage specific patient populations including those with renal impairment, hepatic impairment, cardiac dysfunction, pulmonary toxicity, elderly patients (>65 years), pregnant/nursing women, and women of childbearing potential. Please see pages 8-9

Drug-drug interactions
- Some drugs may have an effect on RYDAPT and, conversely, RYDAPT may affect other drugs if used in the same treatment regimen. Please refer to all relevant safety information to help make strategic treatment decisions. Please see page 7

QTc prolongation
- Increased frequency of QTc prolongation has occurred with RYDAPT, and QT interval should be regularly monitored if RYDAPT is taken concurrently with medicinal products that can prolong QT interval. Please see page 8

Important prescribing and safety information is available on pages 12-15.

NOVARTIS

RYDAPT® midostaurin

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