MOLECULAR TESTING FOR CLINICAL DECISION MAKING

FLT3 MUTATION TESTING IN ACUTE MYELOID LEUKAEMIA

RYDAPT®
midostaurin

FLT3 STATUS IS KEY TO AML PATIENT CARE

WHY?

FLT3 IS SELECTIVE

FLT3 positivity (ITD or TKD) is one of the eligibility criteria for treatment with RYDAPT.

WHEN?

AT DIAGNOSIS

In parallel with cytogenetics.
Results are needed before day 8 of induction chemotherapy.

WHO?

EVERY PATIENT WITH NEWLY DIAGNOSED AML

All patients with newly diagnosed AML should receive a FLT3 test (except promyelocytic leukaemia).

HOW?

IDEALLY BY CAPILLARY ELECTROPHORESIS

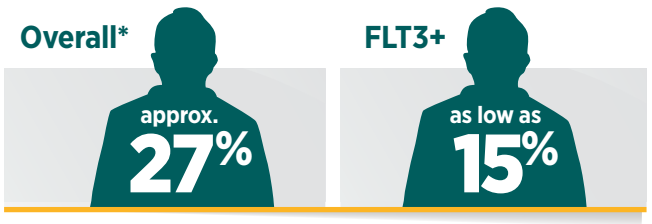
The method used during the RATIFY trial can analyse both mutations (ITD and TKD) in parallel.

FLT3 **mutation testing to identify patients who are potentially eligible for RYDAPT is performed by The Laboratory of Personalized Molecular Medicine GmbH (Germany), a subsidiary of Invivoscribe Technologies, Inc.**

WHY TEST FOR FLT3?

AML HAS ONE OF THE LOWEST SURVIVAL RATES AMONG LEUKAEMIAS[1]

AML survival rates after 5 years[2,3]



Patients who are FLT3 ITD mutation-positive may have a worse prognosis, with higher rates of relapse and lower rates of survival, than patients in the overall AML population[4,5]

*Relative survival based on data of US AML patients from 2007 through 2013.

For decades, there have been few pharmacological advances in AML[4,6]

Standard Chemotherapy†

Patients with newly diagnosed AML who are eligible for intensive chemotherapy unfortunately have not benefitted from approved drug therapy options seen in many other cancers over the past 25 years

RYDAPT + Standard Chemotherapy

†Standard chemotherapy is induction therapy with cytarabine and daunorubicin, and consolidation therapy with high-dose cytarabine.
FLT3, FMS-like tyrosine kinase 3; ITD, internal tandem duplication; TKD, tyrosine kinase domain.

Important prescribing and safety information is available on pages 13-15.

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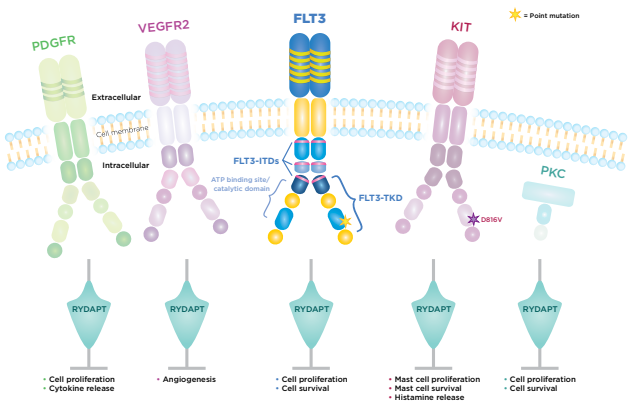
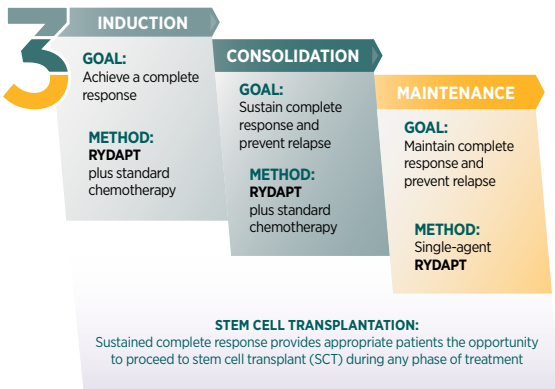
WHY TEST FOR FLT3?

RYDAPT: THE FIRST AND ONLY EMA-APPROVED MULTIKINASE TARGETED INHIBITOR FOR NEWLY DIAGNOSED FLT3+ AML

RYDAPT inhibits **FLT3** and other tyrosine kinases that are drivers of AML[7-12]*



RYDAPT was studied throughout the 3 phases of treatment to help patients with newly diagnosed FLT3+ AML extend survival[7,13]



*Clinical benefit unknown.
ATP, adenosine triphosphate; PDGFR, platelet-derived growth factor receptor; PKC, protein kinase C; VEGFR2, vascular endothelial growth factor receptor-2.

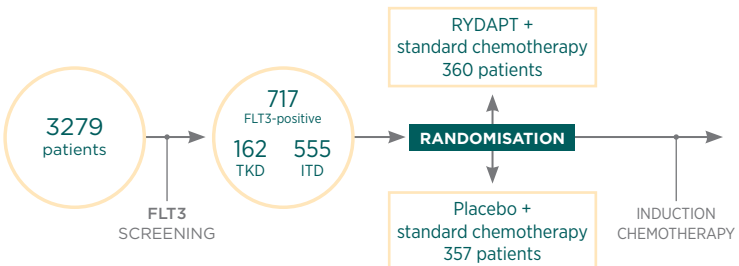
Important prescribing and safety information is available on pages 13-15.

WHY TEST FOR FLT3?

RATIFY IS THE LARGEST CLINICAL EVALUATION IN PATIENTS WITH NEWLY DIAGNOSED FLT3+ AML

RATIFY trial[7,13]

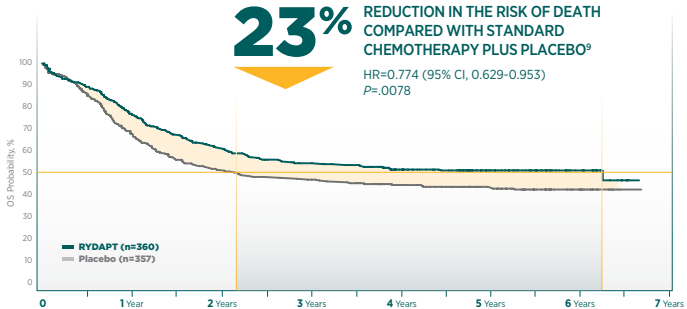
- ✓ Randomised, double-blinded, placebo-controlled
- ✓ Previously untreated adults with newly diagnosed AML <60 years of age



RYDAPT: Significant and sustained survival benefits for patients with newly diagnosed FLT3+ AML[7]

23% REDUCTION IN THE RISK OF DEATH COMPARED WITH STANDARD CHEMOTHERAPY PLUS PLACEBO[9]

HR=0.774 (95% CI, 0.629-0.953)
P=.0078



Safety profile with RYDAPT plus standard chemotherapy[7]

- RYDAPT was generally well tolerated
- The most frequent adverse drug reactions (≥30% incidence) in the RYDAPT plus standard chemotherapy arm were febrile neutropenia (83.4%), nausea (83.4%), exfoliative dermatitis (61.6%), vomiting (60.7%), headache (45.9%), petechiae (35.8%), and pyrexia (34.5%)
- The most frequent grade 3/4 adverse drug reactions were febrile neutropenia (83.5%), lymphopenia (20.0%), device-related infection (15.7%), exfoliative dermatitis (13.6%), hyperglycaemia (7.0%), and nausea (5.8%)
- Serious adverse drug reactions occurred at similar rates in patients in the RYDAPT vs the placebo arm. The most frequent serious adverse drug reaction in both arms was febrile neutropenia (16%)

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WHY TEST FOR FLT3?

FLT3 TESTING SIGNIFICANCE CHANGED FROM PROGNOSTIC IN THE PAST TO SELECTIVE TODAY

FLT3 clinical value

PROGNOSTIC
FLT3 testing in the past

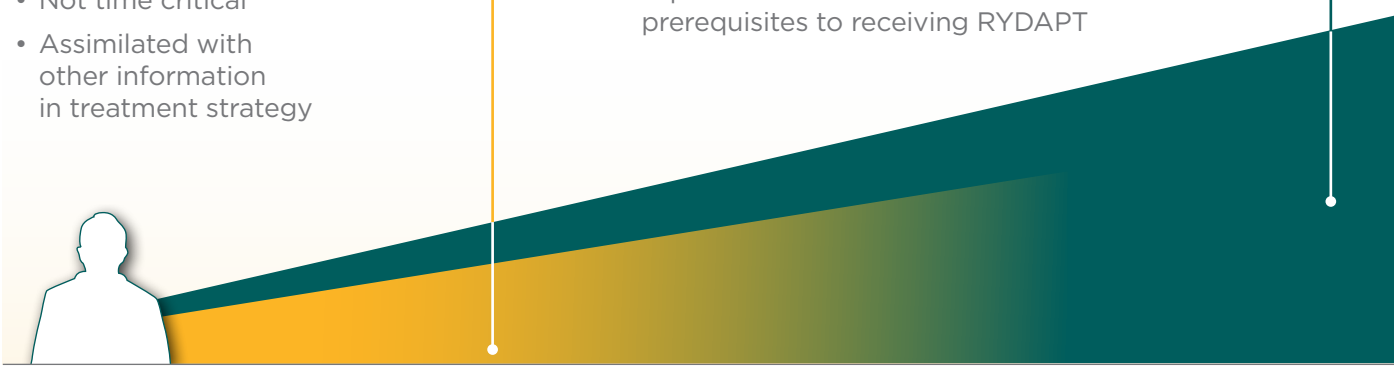
FLT3-**ITD** is important for **prognostication** and is useful for patients with a **normal karyotype**[14]:

- Not time critical
- Assimilated with other information in treatment strategy

SELECTIVE
FLT3 testing today

FLT3-**ITD and TKD** are important to identify potentially eligible patients **regardless of karyotype**[15]:

- Time critical for treatment decision
- Essential for care
- A positive FLT3 mutation result is one of the prerequisites to receiving RYDAPT

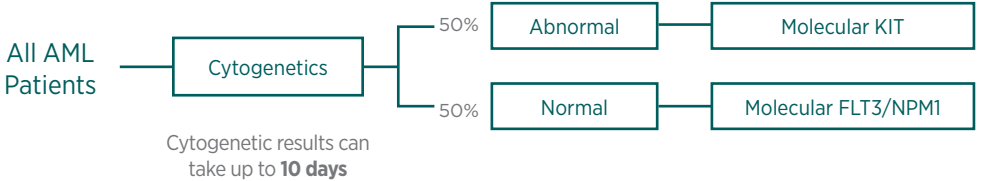


WHO SHOULD BE TESTED FOR FLT3?

TWO TESTING APPROACHES HAVE BEEN APPLIED: SEQUENTIAL AND PARALLEL

Today, both sequential and parallel testing approaches are used for prognosis and risk stratification

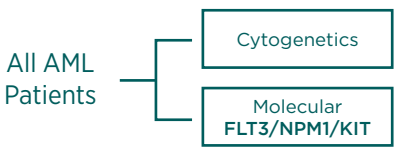
SEQUENTIAL: When cytogenetic tests are performed first and, based on the results, **subsequent molecular testing is only performed on a subset of patients**



SEQUENTIAL

Only 50% of patients with AML receiving a FLT3 test[16]

PARALLEL: When both cytogenetic and molecular tests are performed **at the same time for all patients**



PARALLEL

100% of patients with AML receiving a FLT3 test[16]

All patients with newly diagnosed AML should be tested for FLT3 mutations, irrespective of cytogenetics findings[15]

Important prescribing and safety information is available on pages 13-15.

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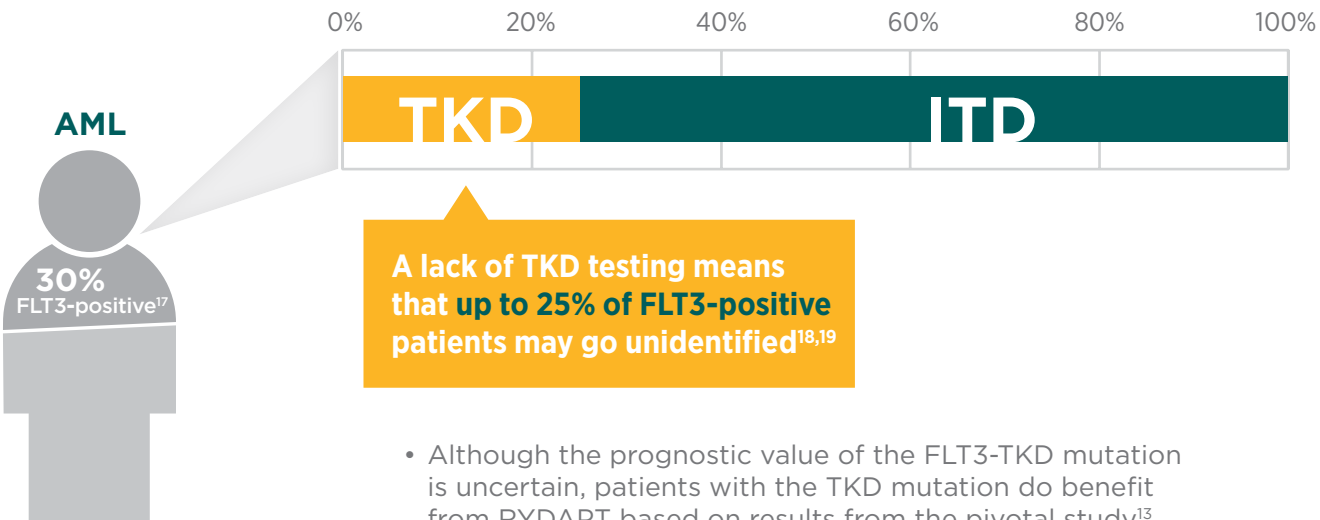
WHO SHOULD BE TESTED FOR FLT3?

FLT3-TKD MUTATIONAL ANALYSIS IS IMPERATIVE; BOTH ITD AND TKD ARE IMPORTANT FOR IDENTIFYING PATIENTS ELIGIBLE FOR RYDAPT

Patients with ITD and TKD mutations were enrolled in the RATIFY trial and both types of patients benefitted from RYDAPT[7,13]



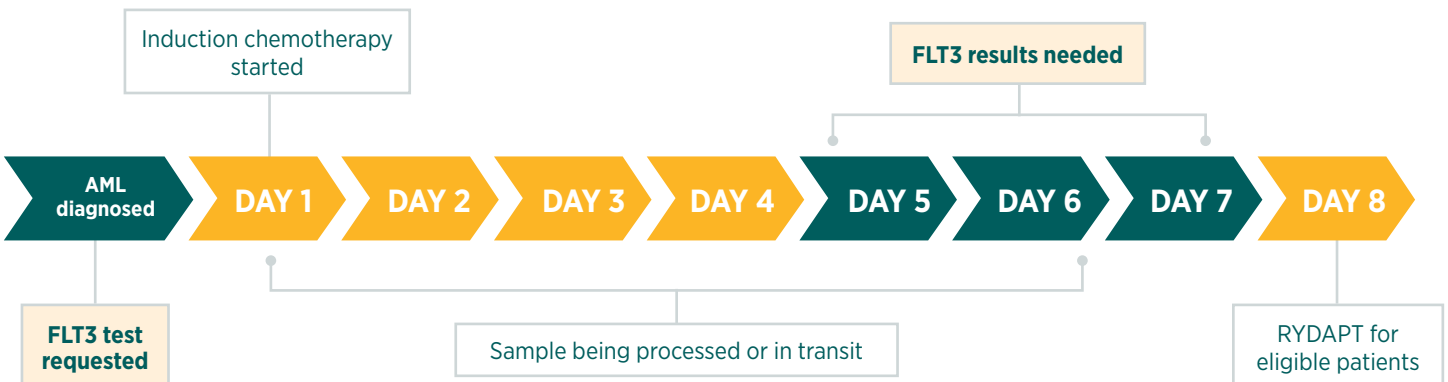
A lack of TKD testing means that up to 25% of FLT3-positive patients may go unidentified[18,19]

- Although the prognostic value of the FLT3-TKD mutation is uncertain, patients with the TKD mutation do benefit from RYDAPT based on results from the pivotal study[13]

WHEN SHOULD THE FLT3 TEST BE PRESCRIBED?

THE FLT3 TEST TURNAROUND TIME IS IMPORTANT TO SUPPORT PATIENT CARE IN THE ACUTE SETTING

According to the RATIFY phase 3 clinical trial, RYDAPT should be administered in sequential combination with induction chemotherapy starting on day 8 for patients with FLT3 mutations (ITD and/or TKD), irrespective of the cytogenetics findings[7]



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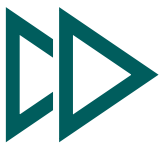
WHEN SHOULD THE FLT3 TEST BE PRESCRIBED?

INTERNATIONAL GUIDELINES RECOGNISE THE CLINICAL VALUE OF A FLT3 TEST AT DIAGNOSIS AS A SELECTIVE MARKER

The latest ELN recommendations (2017) highlight the need for prompt comprehensive FLT3 testing[20]



TEST UP FRONT, AT DIAGNOSIS

Diagnostic workup should include screening for both **FLT3-ITD and -TKD** mutations, together with data on the mutant-to-wild-type allelic ratio

RESULTS ARE NEEDED QUICKLY

At least in patients eligible for intensive chemotherapy, FLT3 mutational screening results should be available, ideally, within **48 to 72 hours**

SELECTIVE RELEVANCE

Patients with newly diagnosed AML and activating FLT3 mutations may be considered to receive **additional therapy with midostaurin**

ELN, European LeukemiaNet.

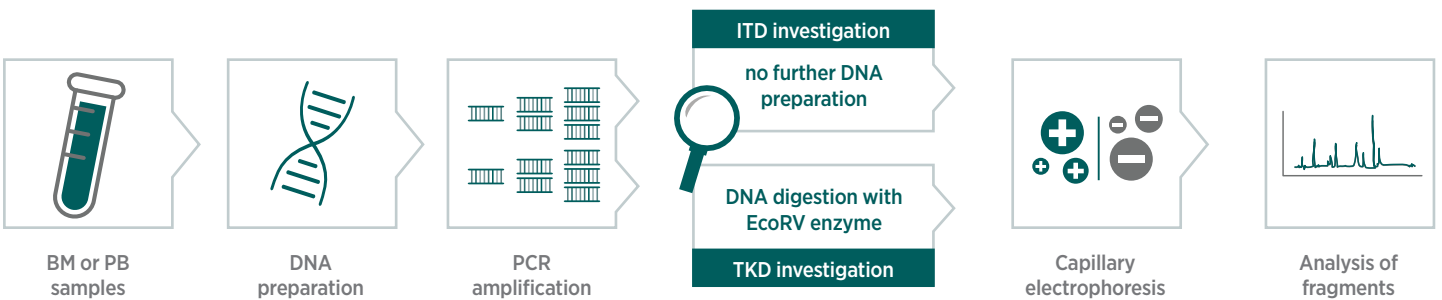
Important prescribing and safety information is available on pages 13-15.

HOW SHOULD THE FLT3 TEST BE BEST PERFORMED?

MULTIPLE METHODOLOGIES ARE CURRENTLY USED FOR FLT3 TESTING IN CLINICAL PRACTICE

The FLT3 test used in the RATIFY clinical trial was based on the Murphy et al. and Thiede et al. methods and analyses for both ITD and TKD mutations by capillary electrophoresis[21-23]

- This approach leads to a more efficient workflow in the lab compared to common methods and could ultimately lead to a faster **determination of FLT3 status**



BM, bone marrow; PB, peripheral blood; PCR, polymerase chain reaction.

- The RATIFY clinical trial assay considers that the FLT3 mutation is **positive** if the mean mutant-to-wild-type **signal ratio** meets or exceeds the **clinical cutoff of 0.05**[21]
- Patients with a signal ratio **less than 0.05 are considered negative** for the FLT3 mutation[21]

REFERENCES

References: 1. Howlader N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2014. Bethesda, MD: National Cancer Institute; 2017. http://seer.cancer.gov/csr/1975_2014/. Updated June 28, 2017. Accessed July 26, 2017. **2.** National Cancer Institute. SEER Cancer Stat Facts: Acute Myeloid Leukemia (AML). http://seer.cancer.gov/statfacts/html/amyl.html. Accessed July 26, 2017. **3.** Fathi AT, Chabner BA. FLT3 inhibition as therapy in acute myeloid leukemia: a record of trials and tribulations. *Oncologist*. 2011;16(8):1162-1174. **4.** Ferrara F, Schiffer CA. Acute myeloid leukaemia in adults. *Lancet*. 2013;381(9865):484-495. **5.** Gale RE, Green C, Allen C, et al; Medical Research Council Adult Leukaemia Working Party. The impact of *FLT3* internal tandem duplication mutant level, number, size, and interaction with *NPM1* mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood.* 2008;111(5):2776-2784. **6.** Lin TL, Levy MY. Acute myeloid leukemia: focus on novel therapeutic strategies. *Clin Med Insights Oncol*. 2012;6:205-217. **7.** RYDAPT [Summary of Product Characteristics]. Novartis Pharma AG; 2017. **8.** Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. *N Engl J Med*. 2005;353(2):172-187. **9.** Rattu MA, Shah N, Iskhakova T, Popovitz B. The utility of FLT3 inhibitors in acute myeloid leukemia. *US Pharm*. 2014;39(11)(Specialty&Oncology suppl):8-11. **10.** Foss B, Ulvestad E, Bruserud Ø. Platelet-derived growth factor (PDGF) in human acute myelogenous leukemia: PDGF receptor expression, endogenous PDGF release and responsiveness to exogenous PDGF isoforms by in vitro cultured acute myelogenous leukemia blasts. *Eur J Haematol*. 2001;67(4):267-278. **11.** Trujillo A, McGee C, Cogle CR. Angiogenesis in acute myeloid leukemia and opportunities for novel therapies. *J Oncol*. 2012;2012:128608. **12.** Altman A, Villalba M. Protein kinase C-θ (PKCθ): it's all about location, location, location. *Immunol Rev*. 2003;192:53-63. **13.** Data on file. Study no. CPKC412A2301. Novartis Pharmaceuticals Corp; 2016. **14.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.2.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed August 28, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. **15.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Myeloid Leukemia V.3.2017. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed July 26, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. **16.** Kumar C. Genetic Abnormalities and Challenges in the Treatment of Acute Myeloid Leukemia. *Genes & Cancer*. 2011;2(2):95-107. **17.** Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012;366(12):1079-1089. **18.** Al-Mawali A. Characteristics and Prognosis of Adult Acute Myeloid Leukemia with Internal Tandem Duplication in the FLT3 Gene. *Oman Medical Journal*. 2013;28(6):432-440. **19.** Santos FP, Jones D, Qiao W, et al. Prognostic value of FLT3 mutations among different cytogenetic subgroups in acute myeloid leukemia. *Cancer*. 2011;117(10): 2145-2155. **20.** 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. **21.** Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a *FLT3* mutation [supplementary appendix published online June 23, 2017]. *N Engl J Med*. 2017. http://www.nejm.org/actionshowSupplements?doi=10.1056%2FNEJMoa1614359&viewType=Popup&viewClass=Suppl. **22.** Murphy K, Levis M, Hafez M, et al. Detection of FLT3 internal tandem duplication and D835 mutations by a multiplex polymerase chain reaction and capillary electrophoresis assay. *J Mol Diagn*. 2003;5(2):96-102. **23.** Thiede C, Steudel C, Mohr B, et al. Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood*. 2002;99(12):4326-4335.

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

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

Warnings and precautions cont'd:

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

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.

RYDAPT®
midostaurin

Important prescribing and safety information is available on pages 13-15.

NOVARTIS

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