

Midostaurin Maintenance Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Midostaurin is indicated as single agent maintenance therapy for adult patients with FLT3 mutation positive acute myeloid leukaemia (AML) in complete response after completion of induction and consolidation chemotherapy.	C92	00661a	CDS: 01/10/2021

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

- For patients in complete remission (by bone marrow evaluation) after four cycles of remission / consolidation therapy (Ref NCCP regimen 00683a Midostaurin and Intermediate Dose Cytarabine Consolidation Therapy), midostaurin is administered every day as single agent maintenance therapy at a dose of 50mg twice daily until relapse for up to 12 cycles of 28 days each.
 - Prior to initiation of midostaurin maintenance therapy, all significant acute toxicity from consolidation therapy must have resolved to < grade 2.
 - Midostaurin maintenance therapy will begin after haematologic recovery (ANC $\geq 1 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$) from remission consolidation, and no sooner than 14 days after the last dose of consolidation.
- In patients receiving a haematopoietic stem cell transplant (SCT), midostaurin should be discontinued 48 hours prior to the conditioning regimen for SCT.

NCCP Regimen: Midostaurin Maintenance Therapy	Published: 28/01/2022 Review: 28/01/2023	Version number: 1
Tumour Group: Leukaemia NCCP Regimen Code: 00661a	IHS Contributor: NCCP Myeloid Clinical Advisory Group	Page 1 of 7
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p style="text-align: center;"><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</i></p>		

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1-28 inclusive	Midostaurin	50mg twice daily	PO	n/a	28 days for up to 12 cycles
Midostaurin capsules should be taken with food at a approximately 12 hour intervals.					
If a dose is missed, the patient should take the next dose at the scheduled time. If vomiting occurs, the patient should not take an additional dose of midostaurin, but should take the next scheduled dose.					

ELIGIBILITY:

- Indication as above
- AML diagnosis with FLT3 mutation confirmed using a validated test excluding FLT 3 positive acute promyelocytic leukaemia

EXCLUSIONS:

- Hypersensitivity to midostaurin
- Concomitant administration of potent CYP3A4 Inducers
- Symptomatic congestive heart failure
- Bilirubin > 2.5 x upper limit of normal

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profiles, magnesium level
- TFT, ECG (QTc interval)
- βhCG pregnancy test

NCCP Regimen: Midostaurin Maintenance Therapy	Published: 28/01/2022 Review: 28/01/2023	Version number: 1
Tumour Group: Leukaemia NCCP Regimen Code: 00661a	IHS Contributor: NCCP Myeloid Clinical Advisory Group	Page 2 of 7

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

Regular tests:

- FBC, renal and liver profiles
- Coagulation profile: APTT, PT, fibrinogen level
- ECG (QTc interval) prior to commencing midostaurin and as clinically indicated thereafter
- LVEF when clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- **Elderly (≥65 years):** No dose adjustment is required in patients aged over 65 years. There is limited experience with midostaurin in AML patients aged 60-70 years and no experience in AML patients above 70 years. In patients aged ≥60 years, midostaurin should be used only in patients eligible to receive intensive induction chemotherapy with adequate performance status and without significant comorbidities.

Haematological:

Table 1: Dose modification of midostaurin in haematological toxicity

ANC ($\times 10^9$ /L)	Dose
<0.5 x 10 ⁹ /L (Grade 4 neutropenia)	Interrupt midostaurin until ANC $\geq 1.0 \times 10^9$ /L, then resume at 50 mg twice daily.
<1.0 x 10 ⁹ /L persisting >2 weeks and suspected to be related to midostaurin	Discontinue midostaurin.

NCCP Regimen: Midostaurin Maintenance Therapy	Published: 28/01/2022 Review: 28/01/2023	Version number: 1
Tumour Group: Leukaemia NCCP Regimen Code: 00661a	IHS Contributor: NCCP Myeloid Clinical Advisory Group	Page 3 of 7

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

Renal and Hepatic Impairment:

Table 2: Dose modification of midostaurin in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment
Midostaurin	No dose adjustment is required for patients with mild or moderate renal impairment. Clinical experience in patients with severe renal impairment is limited and no data are available in patients with end-stage renal disease.	No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. No study has been completed in patients with severe (Child-Pugh C) hepatic impairment.

Management of adverse events:

Table 3: Dose Modification of midostaurin for Adverse Events

Criteria	Midostaurin dosing
Grade 3/4 pulmonary infiltrates	Interrupt midostaurin for the remainder of the cycle. Resume midostaurin at the same dose when infiltrate resolves to Grade ≤ 1 .
Other Grade 3/4 non-haematological toxicities	Interrupt midostaurin until toxicities considered at least possibly related to midostaurin have resolved to Grade ≤ 2 , then resume midostaurin.
QTc interval >470 msec and ≤ 500 msec	Decrease midostaurin to 50 mg once daily for the remainder of the cycle. Resume midostaurin at the initial dose in the next cycle provided that QTc interval improves to ≤ 470 msec at the start of that cycle. Otherwise continue midostaurin 50 mg once daily.
QTc interval >500 msec	Withhold or interrupt midostaurin for the remainder of the cycle. If QTc improves to ≤ 470 msec just prior to the next cycle, resume midostaurin at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer midostaurin during that cycle. Midostaurin may be held for as many cycles as necessary until QTc improves.
Persistent Grade 1/2 toxicity	Persistent Grade 1 or 2 toxicity that patients deem unacceptable may prompt an interruption for as many as 28 days.

NCCP Regimen: Midostaurin Maintenance Therapy	Published: 28/01/2022 Review: 28/01/2023	Version number: 1
Tumour Group: Leukaemia NCCP Regimen Code: 00661a	IHS Contributor: NCCP Myeloid Clinical Advisory Group	Page 4 of 7

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate to high (**Refer to local policy**). **PREMEDICATIONS:** None usually required

OTHER SUPPORTIVE CARE:

- Proton pump Inhibitor (**Refer to local policy**)
- Anti-viral prophylaxis (**Refer to local policy**)
- Anti-fungal prophylaxis: No standard antimicrobial prophylaxis is recommended during maintenance treatment, unless there are patient specific arguments to do so.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia and infections:** Neutropenia has occurred in patients receiving midostaurin as monotherapy and in combination with chemotherapy. White blood cell counts (WBCs) should be monitored regularly, especially at treatment initiation. In patients who develop unexplained severe neutropenia beyond what is usually expected in AML in remission, treatment with midostaurin should be interrupted until ANC is $\geq 1.0 \times 10^9/L$. Midostaurin should be discontinued in patients who develop recurrent or prolonged severe neutropenia that is suspected to be related to midostaurin. Any active serious infection should be under control prior to starting treatment with midostaurin monotherapy.
- **Cardiac dysfunction:** Patients with symptomatic congestive heart failure were excluded from clinical studies. In patients at risk, midostaurin should be used with caution and the patient closely monitored by assessing LVEF when clinically indicated (at baseline and during treatment). An increased frequency of QTc prolongation was noted in midostaurin-treated patients, however, a mechanistic explanation for this observation was not found. Caution is warranted in patients at risk of QTc prolongation (e.g. due to concomitant medicinal products and/or electrolyte disturbances). Interval assessments of QT by ECG should be considered if midostaurin is taken concurrently with medicinal products that can prolong QT interval.

NCCP Regimen: Midostaurin Maintenance Therapy	Published: 28/01/2022 Review: 28/01/2023	Version number: 1
Tumour Group: Leukaemia NCCP Regimen Code: 00661a	IHS Contributor: NCCP Myeloid Clinical Advisory Group	Page 5 of 7

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

- **Pulmonary toxicity:** Interstitial lung disease (ILD) and pneumonitis, in some cases fatal, have occurred in patients treated with midostaurin monotherapy or in combination with chemotherapy. Patients should be monitored for pulmonary symptoms indicative of ILD or pneumonitis and midostaurin discontinued in patients who experience pulmonary symptoms indicative of ILD or pneumonitis that are \geq Grade 3 (NCI CTCAE).
- **Embryofetal toxicity:** Pregnant women should be informed of the potential risk to a foetus; females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with midostaurin and to use effective contraception during treatment with midostaurin and for at least 4 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception.
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy (**Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- 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 midostaurin.
 - Concomitant use of midostaurin with strong inducers of CYP3A4 (e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort [*Hypericum perforatum*]) is contraindicated - strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites.
 - Strong CYP3A4 inhibitors such as azole antifungals may increase midostaurin blood concentrations.
- It is currently unknown whether midostaurin may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception.
- Current drug interaction databases should be consulted for more information.

NCCP Regimen: Midostaurin Maintenance Therapy	Published: 28/01/2022 Review: 28/01/2023	Version number: 1
Tumour Group: Leukaemia NCCP Regimen Code: 00661a	IHS Contributor: NCCP Myeloid Clinical Advisory Group	Page 6 of 7
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</i></p>		

REFERENCES:

1. Stone RM et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. *N Engl J Med.* 2017 Aug 3;377(5):454-464. doi: 10.1056/NEJMoa1614359. Epub 2017 Jun 23. PMID: 28644114; PMCID: PMC5754190.
2. Midostaurin (Rydapt®) Summary of Product Characteristics. Accessed July 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/rydapt-epar-product-information_en.pdf
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf>

Version	Date	Amendment	Approved By
1	28/01/2022		NCCP Myeloid Clinical Advisory Group

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

NCCP Regimen: Midostaurin Maintenance Therapy	Published: 28/01/2022 Review: 28/01/2023	Version number: 1
Tumour Group: Leukaemia NCCP Regimen Code: 00661a	IHS Contributor: NCCP Myeloid Clinical Advisory Group	Page 7 of 7
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens</i></p>		