Midostaurin Maintenance Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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

*This is for post 2012 indications only

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 patients 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 **≥ 1 x10^9/L**, platelet count **≥ 100 x 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.

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 approximately 12 hour intervals. The capsules should be swallowed whole with a glass of water. They should not be opened, crushed or chewed to ensure proper dosing and avoid the unpleasant taste of the capsule content.					
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
- Pregnancy / Lactation

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)
- ßhCG pregnancy test

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. 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 ($x10^9$/L)	Dose
<0.5 x 10^9/L (Grade 4 neutropenia)	Interrupt midostaurin until ANC ≥1.0 x 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.

Renal and Hepatic Impairment:

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

Drug	Renal Impairment	Hepatic Impairment
Midostaurin	CrCl ≥ 30ml/min: no dose adjustment is needed CrCl < 30ml/min: no need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected	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. Mild / moderate (Child-Pugh A and B): no dose adjustment Severe or Child Pugh C: not recommended

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 msecs and ≤500 msecs	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 msecs at the start of that cycle. Otherwise continue midostaurin 50 mg once daily.
QTc interval >500 msecs	Withhold or interrupt midostaurin for the remainder of the cycle. If QTc improves to ≤470 msecs 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.

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 ≥1.0 x 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.
- **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 ≥ Grade 3 (NCI CTCAE).
- **Embryofoetal 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.
- **Breast-feeding:** Breast-feeding should be discontinued during treatment with midostaurin and for at least four months after stopping treatment.
- **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.
- Midostaurin is a mild inducer of CYP2B6. Medicinal products with a narrow therapeutic range that are substrates of CYP2B6 (e.g. bupropion or efavirenz) should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.
- Midostaurin is a mild inhibitor of BRCP substrates. Medicinal products with a narrow therapeutic range that are substrates of the transporter BCRP (e.g. rosuvastatin or atorvastatin) should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.
- Current drug interaction databases should be consulted for more information.

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. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019; 20:e201-08. https://doi.org/10.1016/S1470-2045(19)30145-7
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
4. Midostaurin (Rydapt®) Summary of Product Characteristics. Last updated 11/05/2023. Accessed July 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/rydapt-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	28/01/2022		NCCP Myeloid Clinical Advisory Group
2	08/12/2023	Reviewed. Amended treatment table (footnotes). Updated exclusions and dose modifications (re: elderly patients). Updated dose modification in renal/hepatic impairment. Updated adverse effects and drug interactions.	Dr. Eibhlin Conneally

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.