Midostaurin and Intermediate Dose Cytarabine Consolidation Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Midostaurin is indicated in combination with intermediate dose cytarabine consolidation chemotherapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive.	C92	00683a	Midostaurin: CDS 01/10/2021 Cytarabine: Hospital

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.

- Patients who achieve complete remission after one cycle of induction therapy with Midostaurin and DAUNOrubicin and Cytarabine Induction Therapy (Ref NCCP Regimen 00682a) may at the discretion of the prescribing Consultant either:
  - Receive a second cycle of induction treatment (Ref NCCP Regimen 00682a).

  and
  - **Two** cycles of consolidation therapy (described below) at the discretion of the prescribing consultant.

  OR
  - Receive **three** cycles of consolidation therapy (described below) at the discretion of the prescribing Consultant.

  Patients should generally receive a total of 4 cycles of treatment between the induction and consolidation cycles (e.g. 2+2 or 1+3).

- Consolidation treatment is administered as detailed in the treatment table.

- Each consolidation cycle is four weeks in duration, and should begin within two weeks following hematologic recovery (ANC ≥ **1x10^9**/L, platelet count ≥ **100 x 10^9**/L), but not sooner than four weeks from the beginning of the previous cycle.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 3 and 5	Cytarabine	1500mg/m^2 **AM**	IV infusion	500ml NaCl 0.9% over 4 hours	Every 28 days for 2 to 3 cycles (see above)
2	1, 3 and 5	Cytarabine	1500mg/m^2 **PM** (12 hours after start of **AM** infusion)	IV infusion	500ml NaCl 0.9% over 4 hours	Every 28 days for 2 to 3 cycles (see above)
3	8 to 21 inclusive	Midostaurin	50mg twice daily	PO	n/a	Every 28 days for 2 to 3 cycles(see above)
Patients aged ≥ 61 years should receive cytarabine 1000 mg/m^2 TWICE a day						
Midostaurin capsules should be taken with food at 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 cytarabine, midostaurin or any of the excipients
- 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
- Chest x-ray
- TFT, ECG (QTc interval)
- MUGA or ECHO
- Virus serology: cytomegalovirus(CMV) infection, HIV (human immunodeficiency virus), hepatitis B (HBsAg, HBcoreAb), C.
  *Hepatitis B reactivation: See Adverse effects/ Regimen specific complications
- ßhCG pregnancy test

Regular tests:

- FBC, renal and liver profiles
- Coagulation profile: APTT, PT, fibrinogen level
- ECG (QTc interval) Day 8 (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 of midostaurin 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.

Renal and Hepatic Impairment:

Table 1: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
Cytarabine	**CrCl (mls/min)**	**Dose**	If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.
	>60	100%	
	45-60	60%	
	31-45	50%	
	<30	omit	
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 2: 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.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Cytarabine: Moderate **(Refer to local policy)**

Midostaurin: Moderate to High **(Refer to local policy)**

PREMEDICATIONS:

Cytarabine:

To prevent a chemical induced conjunctivitis developing with cytarabine, Prednisolone eye drops (e.g. Pred Mild) 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be administered.

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy).** Strong CYP3A4 inhibitors (e.g. posaconazole) can increase midostaurin exposure. If concomitant use is required, an ECG should be performed prior to commencement of the CYP3A4 inhibitor to assess the QTc and QTc should continue to be monitored by regular ECGs. In addition, monitoring of posoconazole levels is recommended.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

Midostaurin:

Midostaurin is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **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 , 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.
- **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.

Cytarabine:

- **Cytarabine syndrome:** Treatment with cytarabine may cause a 'Cytarabine Syndrome' characterised by flu-like symptoms, skin rash and occasionally chest pain.
- **Myelosuppression:** Cytarabine is a potent bone marrow suppressant. Patients receiving this drug must be under close medical supervision and should have leucocyte and platelet counts performed daily.
- **Neurotoxicity:** This may occur in patients treated with high dose cytarabine. Assess cerebellar function prior to each cytarabine dose. The risk of neurotoxicity is enhanced in the presence of renal impairment. Ensure that dose of cytarabine is adjusted in renal impairment.

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.

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. Cytarabine Solution for Injection Summary of Product Characteristics. Accessed July 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0540-096-001_28062019145807.pdf
3. 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
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
6. 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.

[i] 'This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.'