Midostaurin plus Chemotherapy (daunorubicin & cytarabine induction chemotherapy followed by high dose cytarabine consolidation chemotherapy), followed by midostaurin monotherapy as maintenance for Acute Myeloid Leukemia with a *FLT3* Mutation

Indication	For treating FLT3 mutation positive untreated acute myeloid leukaemia in adults. NB Patients must be in complete remission to receive midostaurin monotherapy as maintenance treatment.
Treatment Intent	Disease modification
Frequency and number of cycles	Given on days 8-21 of all cycles of induction and consolidation chemotherapy. In the maintenance monotherapy phase, a maximum of 12 x 28-day cycles of midostaurin will be used
Monitoring parameters and management of adverse events & dose reductions	• Monitor FBC, U&Es and LFTs at each cycle. In-particular ALT, sodium and calcium. FBC should be monitored regularly at treatment initiation. • During induction and consolidation, blood parameters must meet those required for chemotherapy. • During maintenance treatment neuts must be >/=0.5 • In patients who develop unexplained severe neutropenia, 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. • <u>Missed doses of midostaurin:</u> 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. • <u>Renal impairment:</u> No dose adjustment is required in 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. • <u>Hepatic impairment:</u> No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. No data in severe (Child-Pugh C) hepatic impairment • <u>Drug interactions</u>: Concomitant administration of potent CYP3A4 inducers, (rifampicin, St. John's Wort , carbamazepine, enzalutamide, phenytoin) is contraindicated. Caution with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin). Drugs with a narrow therapeutic range that are substrates of CYP1A2 (e.g. tizanidine), CYP2D6 (e.g. codeine), CYP2C8 (e.g.

	paclitaxel), CYP2C9 (e.g. warfarin), CYP2C19 (e.g. omeprazole), CYP2E1 (e.g. chlorzoxazone), CYP3A4/5 (e.g. tacrolimus), CYP2B6 (e.g. efavirenz), P-gp (e.g. paclitaxel), BCRP (e.g. atorvastatin) or OATP1B1 (e.g. digoxin) should be used with caution when administered concomitantly with midostaurin and may need dose adjustment to maintain optimal exposure. • <u>Cautions:</u> • Patients at risk of cardiac dysfunction should be treated with caution and the patient closely monitored by assessing LVEF when clinically indicated (at baseline and during treatment). 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 taken concurrently with medicinal products that can prolong QT interval. • 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. • 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. • Because of the potential for serious adverse reactions in breast-feeding infants from Midostaurin, women should discontinue breast-feeding during treatment with Midostaurin and for at least 4 months after stopping treatment • Midostaurin has minor influence on the ability to drive and use machines. Dizziness and vertigo have been reported in patients taking Midostaurin and should be considered when assessing a patient's ability to drive or use machines. • If the patient proceeds to a stem cell transplant, midostaurin will be permanently discontinued prior to the stem cell transplant conditioning regimen
Reference(s)	Rydapt SpC accessed on-line 10/5/18

NB For funding information, refer to the SACT funding spreadsheet

Dosed on days 8-21 of induction (up to 2 cycles) and consolidation (up to 4 cycles)
To be prescribed with DA (daunorubicin and cytarabine) induction and high dose cytarabine consolidation

TTO MEDICATION	Drug	Dose	Route	Directions
Days 8-21	Midostaurin	50mg	po	Swallowed whole with a glass of water twice daily at approximately 12-hour intervals for 14 days. Take with food. Do not open, crush or chew.
REVIEW CHEMOTHERAPY PRESCRIPTION AND DELETE IF NOT REQUIRED	Metoclopramide	10mg	po	Up to three times a day for three days then 10mg up to three times a day when required. Do not take for more than 5 days continuously.

For patients in complete response, maintenance treatment every 28 days for a maximum of 12 cycles

TTO MEDICATION	Drug	Dose	Route	Directions
Days 1-28	Midostaurin	50mg	po	Swallowed whole with a glass of water twice daily at approximately 12-hour intervals for 28 days. Take with food. Do not open, crush or chew.
	Metoclopramide	10mg	po	Up to three times a day for three days then 10mg up to three times a day when required. Do not take for more than 5 days continuously.

Table 1 Midostaurin dose interruption, reduction and discontinuation recommendations in patients with AML

Phase	**Criteria**	**Midostaurin dosing**
Induction, consolidation and maintenance	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.
Maintenance only	Grade 4 neutropenia (ANC <0.5 x 10^9/l)	Interrupt Midostaurin until ANC ≥1.0 x 10^9/l, then resume at 50 mg twice daily. If neutropenia (ANC <1.0 x 10^9/l) persists >2 weeks and is suspected to be related to Midostaurin, discontinue Midostaurin.
	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.