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| **Indication** | Monotherapy treatment of aggressive systemic mastocytosis (ASM), aggressive systemic mastocytosis with an associated haematological neoplasm (ASM-AHN) and mast cell leukaemia (MCL).<br><br>Patients must not have previously received treatment with midostaurin.<br><br>NB separate protocol for use in patients with FLT3-mutation-positive Acute Myeloid Leukaemia |
| **Treatment Intent** | Disease modification |
| **Frequency and number of cycles** | Every 28 days<br><br>Until disease progression or excessive toxicity or patient choice to discontinue.<br><br>A formal medical review should be scheduled to occur by at least the end of the second cycle to assess tolerability and whether treatment should continue. |
| **Monitoring Parameters pre-treatment** | • Monitor FBC, U&Es and LFTs at each cycle.<br>• The risk of hyperglycaemia has been linked to midostaurin. Blood sugar monitoring should be monitored throughout treatment and patients with diabetes should be advised to closely monitor their blood sugars and liaise with their diabetic team.<br>• All patients should have baseline ECG to assess QTC interval and as clinically indicated throughout treatment.<br>• **Hepatic impairment:** 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: not recommended.<br>• **Renal impairment:** 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.<br>• 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.<br>• ***Cardiac toxicity:** 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 in patients at risk of QTc prolongation (e.g. due to concomitant medicinal products and/or electrolyte disturbances).<br>If QTc interval is >500msec, withhold until QTC is <500msec. Resume treatment at 50mg twice a day and increase to 100mg twice a day if tolerated.<br>Discontinue if toxicity does not resolve within 21 days or recurs at reduced dose of midostaurin. Interval assessments of QT by ECG should be considered if midostaurin taken concurrently with medicinal products that can prolong QT interval. Check potassium and magnesium levels and correct any abnormalities.<br>• **Dose Modifications: see table 1**<br>• **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**<br>• 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 |

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| | concomitantly with midostaurin and may need dose adjustment to maintain optimal exposure.<br>• **Missed dose:** 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, but should take the next scheduled dose.<br>• For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet.<br>• 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. |
| **References** | SPC accessed online 01.09.21 Blueteq form accessed on line 01.09.21 KMCC protocol HAEM-AML-028 V1 CDF list accessed online 01.09.21 v1.186 |

NB For funding information, refer to CDF and NICE Drugs Funding List

**Table 1 Dose interruption, reduction and discontinuation recommendations**

| **Criteria** | **Modification** |
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| ANC <1.0 x $10^9$/l attributed to midostaurin in patients without MCL, or ANC less than 0.5 x $10^9$/l attributed to midostaurin in patients with baseline ANC value of 0.5-1.5 x $10^9$/l | Interrupt until ANC ≥1.0 x $10^9$/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily.<br>Discontinue if low ANC persists for >21 days and is suspected to be related to midostaurin. |
| Platelet count less than 50 x $10^9$/l attributed to midostaurin in patients without MCL, or platelet count less than 25 x $10^9$/l attributed to midostaurin in patients with baseline platelet count of 25-75 x $10^9$/l | Interrupt until platelet count greater than or equal to 50 x $10^9$/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily.<br>Discontinue if low platelet count persists for >21 days and is suspected to be related to midostaurin. |
| Haemoglobin less than 80 g/L attributed to midostaurin in patients without MCL, or life-threatening anaemia attributed to midostaurin in patients with baseline haemoglobin value of 80-100 g/L | Interrupt until haemoglobin greater than or equal to 80 g/L, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily.<br>Discontinue if low haemoglobin persists for >21 days and is suspected to be related to midostaurin. |
| Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy | Interrupt for 3 days (6 doses), then resume at 50 mg twice daily and, if tolerated, gradually increase to 100 mg twice daily. |
| Other Grade 3/4 non-haematological toxicities | Interrupt until event has resolved to Grade ≤2, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily.<br>Discontinue if toxicity is not resolved to Grade ≤2 within 21 days or severe toxicity recurs at a reduced dose. |
| ANC: Absolute Neutrophil Count<br>CTCAE severity: Grade 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms. | |

**Repeat every 28 days**

| TTO | Drug | Dose | Route | Directions |
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| Day 1 | **MIDOSTAURIN** | **100mg** | PO | Swallowed whole with a glass of water twice daily at approximately 12-hour intervals for 28 days.<br>Take with food. Do not open, crush or chew.<br>Available as 25mg capsule. |
| | Metoclopramide | 10mg | PO | 10mg TDS PRN. Do not take for more than 5 days continuously.<br>*see cardiac toxicity notes above. |
| | Allopurinol | 300mg | PO | OD for 1 week only. |
| | Aciclovir | 400mg | PO | Twice daily. Consider if neutrophil count is <1 x $10^9$/l |