Thames Valley
Strategic Clinical Network

MIDOSTAURIN (ASM)

INDICATION

Monotherapy for advanced systemic mastocytosis - split into 3 subtypes: aggressive systemic mastocytosis (**ASM**), systemic mastocytosis with associated haematological neoplasm (**SM-AHN**) or mast cell leukaemia (**MCL**). **(NICE TA 728 - Blueteq required)**

Patients established on an early access/compassionate use programme will continue to receive their supplies through this route.

Available as 25mg capsules only.

Separate protocol exists for Midostaurin in Acute Myeloid Leukaemia

---

TREATMENT INTENT

Disease Modification

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, U&Es, LDH, urate, calcium, creatinine, LFTs, glucose, **mast cell tryptase,** Hepatitis B core antibody and Hepatitis B surface Ag, Hepatitis C antibody. Consider additional virology in selected patients.
2. Ensure bone marrow findings and other investigations confirm diagnosis and are documented in notes prior to administration of therapy.
3. Urine pregnancy test - before cycle 1 of each new therapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy
4. ECG at baseline
5. ECHO or MUGA if there is history or risk factors of congestive heart failure
6. Record performance status (WHO/ECOG)
7. Record height and weight
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment
9. Treatment should be agreed in the relevant MDT
10. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures

---

DRUG REGIMEN / CYCLE FREQUENCY

MIDOSTAURIN 100mg PO twice daily continuously

Capsules should be taken **with/after food**. If a dose is missed or vomiting occurs, no additional dose is required and the next dose should be taken at the scheduled time.

Treatment breaks of 3 months are allowed.

RESTAGING

Discontinue treatment if there is a lack of major or partial response after 2 cycles.

DOSE MODIFICATIONS

Renal Impairment	Hepatic Impairment
No dose adjustment is required for patients with any level of renal impairment.	Mild or moderate (Child-Pugh A or B) hepatic impairment: No dose adjustment required Severe hepatic impairment (Child-Pugh C): Not recommended

Haematological Toxicity

Count	Action
ANC < 1 x 10^9/L attributed to midostaurin in patients without MCL, or ANC < 0.5 x 10^9/L attributed to midostaurin in patients with baseline ANC value of 0.5-1.5 x 10^9/L	Withhold midostaurin until ANC ≥ 1 x10^9/L and resume at 50mg twice a day. Increase to 100mg twice a day if tolerated. Discontinue midostaurin if low ANC persists for >21 days and is suspected to be midostaurin related. Consider BM to exclude cytopenias due to disease
Platelet < 50 x 10^9/L attributed to midostaurin in patients without MCL, or Platelet < 25 x 10^9/L attributed to midostaurin in patients with baseline platelet count of 25-75 x 10^9/L	Withhold midostaurin until platelet ≥ 50 x10^9/L and resume at 50mg twice a day. Increase to 100mg twice a day if tolerated. Discontinue midostaurin if low platelet count persists for >21 days and is suspected to be midostaurin related. Consider BM to exclude cytopenias due to disease
Haemoglobin <80g/L attributed to midostaurin in patients without MCL, or Life-threatening anaemia attributed to midostaurin in patients with baseline haemoglobin value of 80-100g/L	Withhold midostaurin until haemoglobin ≥80g/L and resume at 50mg twice a day. Increase to 100mg twice a day if tolerated. Discontinue midostaurin if low haemoglobin persists for >21 days and is suspected to be midostaurin related. Consider BM to exclude cytopenias due to disease

Non-Haematological Toxicity

Cardiac Toxicity

QT prolongation	**For QTc interval > 500 msec,** Withhold midostaurin until QTc interval ≤ 500 msec. Resume at 50mg twice a day and increase to 100mg twice a day if tolerated. Discontinue midostaurin if toxicity is not resolved within 21 days or severe toxicity recurs at a reduced dose of midostaurin. Check magnesium and potassium levels and correct any abnormalities. If possible, discontinue any other QT prolonging medication. Consider referral to cardiology.

Nausea

Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy	Withhold midostaurin for 3 days (6 doses), then resume at 50 mg twice daily. Gradually increase to 100 mg twice daily if tolerated.

Any other toxicities

Other Grade 3/4 non-haematological toxicities	Withhold midostaurin until event has resolved to Grade ≤2 and resume at 50mg twice a day. Increase to 100mg twice a day if tolerated. Discontinue midostaurin if toxicity has not resolved to Grade ≤2 within 21 days or if severe toxicity recurs at a lower dose.

INVESTIGATIONS

- FBC, U&E, LFT, serum amylase and serum lipase, mast cell tryptase monthly, until stable, then repeat every 3 monthly
- Consider serial ECG monitoring in patients at risk of QTc prolongation

CONCURRENT MEDICATION

ALLOPURINOL	300mg PO once daily for 7 days on cycle 1
ACICLOVIR	200mg PO three times a day when the neutrophil count is $<1x10^9$/L
ANTI-EMETIC	Ondansetron, metoclopramide or cyclizine. Consider QT prolongation risk with ondansetron or metoclopramide

EMETIC RISK

Moderate

DRUG INTERACTIONS

Concomitant strong CYP3A4 inducers (e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort etc) are contraindicated.

Caution is required with strong CYP3A4 inhibitors because they can increase the plasma concentrations of midostaurin. Consider alternative medicinal products that do not strongly inhibit CYP3A4 activity. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.

Hormonal contraceptives- It is currently unknown whether midostaurin may reduce their effectiveness. Women using hormonal contraceptives should add a barrier method of contraception

Caution with drugs that prolong QT interval – regular assessments of QTc by ECG should be considered if midostaurin is taken concurrently with QT prolonging drugs

---

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Febrile neutropenia, thrombocytopenia, anaemia, leucopenia, infections, , nausea, vomiting, diarrhoea, fatigue, headache, dizziness & vertigo, electrolyte imbalance, deranged LFTs, elevated serum lipase, hyperglycaemia, hypotension, peripheral oedema, pulmonary toxicity (pneumonitis/ILD).

QT prolongation - use with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:

- with congenital long QT prolongation
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.
- Taking anti-arrhythmic medicinal products or other substances that lead to QT prolongation

---

TREATMENT-RELATED MORTALITY

Extremely rare (<1%)

REFERENCES

1. Novartis. Rydapt 25mg soft capsules summary of product characteristics. Updated 04/02/2021. Accessed via http://www.medicines.org.uk/emc on 25/10/2021
2. NICE TA 728. Midostaurin for treating advanced systemic mastocytosis. Published 22/09/2021. Accessed 25/10/2021 via http://www.nice.org.uk/ta728.
3. Krens S D et al (2019). Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol*; **20:** e201–08

REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	New document	April 2017	1.0	
Cheuk-kie Jackie Cheung (Haematology Pharmacist)	New indication and funding added for UK license	Feb 2019	1.1	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. NSSG Myeloid Group	Annual protocol meeting. Separation of Midostaurin for AML and other indications. Protocol renamed.	Oct 2019	1.2	Oct 2021
Yen Lim, Haematology Pharmacist. NSSG Myeloid Group	Addition of NICE TA/Blueteq requirements. Updated in line with SPC. Annual protocol meeting.	Nov 2021	2.0	Nov 2023