PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Midostaurin

Aggressive systemic mastocytosis, systemic mastocytosis with associated haematological neoplasm or mast cell leukaemia in adults

PROTOCOL REF: MPHAASMSM

(Version No. 1.0)

****NB there is also a protocol for midostaurin in AML. Make sure you are looking at the correct document before proceeding****

Approved for use in:

- Aggressive Systemic Mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-ASM) or Mast Cell Leukaemia (MCL) in patients with an ECOG of 0-3 as monotherapy
- As per NHS England guidance patients on the early access/compassionate use scheme prior to NHSE approval will remain on this scheme and will not be transferred to commercial stock.

************A blueteq form is required***********

Dosage:

Drug	Dosage	Route	Frequency
Midostaurin	100mg	Oral	Twice daily at approximately 12-hour intervals

Midostaurin will continue until progression or unacceptable toxicity

Administration:

- 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.
- The capsules should be taken with a meal to increase absorption
- 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.
- Midostaurin contains 666 mg of alcohol (ethanol) in each 200 mg dose (maximum daily dose), which is equivalent to 14 vol. % ethanol anhydrous. The amount in a 200 mg dose of this medicine is equivalent to 16.9 ml beer or 7.0 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects. Alcohol may be harmful in patients with alcohol related problems, epilepsy or liver problems or during pregnancy or breast feeding

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Non-applicable

Interactions:

Midostaurin undergoes extensive hepatic metabolism mainly through CYP3A4 enzymes which are either induced or inhibited by a number of concomitant medicinal products.

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 because strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites (CGP52421 and CGP62221).

Strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin) may increase midostaurin concentrations. If concurrent use is unavoidable then patients should be monitored closely for adverse effects.

Medicinal products 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.

For more detailed interactions please refer to the SPC and add a link to the appropriate SPC

Main toxicities:
The most frequent ADRs were nausea (82%), vomiting (68%), diarrhoea (51%), peripheral oedema (35%) and fatigue (31%). The most frequent Grade 3/4 ADRs were fatigue (8.5%), sepsis (7.7%), pneumonia (7%), febrile neutropenia (7%), and diarrhoea (6.3%). The most frequent non-haematological laboratory abnormalities were hyperglycaemia (93.7%), total bilirubin increased (40.1%), lipase increased (39.4%), aspartate aminotransferase (AST) increased (33.8%), and alanine aminotransferase (ALT) increased (33.1%), while the most frequent haematological laboratory abnormalities were absolute lymphocyte count decreased (73.2%) and ANC decreased (58.5%). The most frequent Grade 3/4 laboratory abnormalities were absolute lymphocyte count decreased (45.8%), ANC decreased (26.8%), hyperglycaemia (19%), and lipase increased (17.6%)

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X			X**	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
On treatment review					
FBC	X	X	X	X	Every cycle (can be extended to every 12 weeks in stable patients)
U&E & LFTs & Magnesium	X	X	X	X	Every cycle (can be extended to every 12 weeks in stable patients)
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle (can be extended to every 12 weeks in stable patients)
Mast cell tryptase levels	X	X	X	X	Monthly for the first 6/12 then can be extended to 3 monthly if clinically indicated
CT abdo/US abdo scan	X				As clinically indicated
Dexa (bone density) scan					To be done every three years in SM patients (on or off treatment)
ECG					If clinically indicated
Blood pressure measurement	X				Repeat if clinically indicated
Respiratory Rate					If clinically indicated
Weight recorded	X	X	X	X	Every cycle
Blood glucose	X	X	X	X	Every cycle
Pregnancy test	X				If clinically indicated
Height	X				

Dose Modifications and Toxicity Management:

Haematological toxicity:

Criteria	Dose adjustment
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 midostaurin until ANC ≥1.0 x 10^9/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue midostaurin 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 midostaurin until platelet count greater than or equal to 50 x 10^9/L, then resume midostaurin at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue midostaurin 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 midostuarin in patients with baseline haemoglobin value of 80-100 g/L	Interrupt midostaurin until haemoglobin greater than or equal to 80 g/L, then resume midostaurin at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue midostaurin if low haemoglobin persists for >21 days and is suspected to be related to midostaurin.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Dosing in renal and hepatic impairment:

Renal	Renal elimination is a minor route of elimination for midostaurin. Mild to moderate renal impairment (CrCl ≥ 30 ml/min): no dose adjustment is required. Severe renal impairment (15 ≤ CrCL < 30 ml/min): limited clinical experience in this patient group, consult clinical team. End-stage renal disease (CrCl < 15ml/min) no data are available, consult clinical team.

Hepatic	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.

Parameters	1 point	2 points	3 points
Total bilirubin (µmol/L)	< 34	34–50	> 50
Serum albumin (g/L)	> 35	28–35	< 28
Prothrombin time, prolongation (s) *Or* INR	< 4 < 1.7	4–6 1.7-2.3	> 6 >2.3
Ascites	None	Mild to Moderate (diuretic responsive)	Severe (diuretic refractory)

	Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory to medication)

INR: International Normalised Ratio.
Child-Pugh Class A = 5-6 points
Child-Pugh Class B = 7-9 points
Child-Pugh Class C = 10 or more points
Please note: assessment of Child-Pugh Class is to help guide clinical teams when prescribing and pharmacists when screening.

References:

1. https://www.medicines.org.uk/emc midostaurin. Revised 11/5/22. Accessed 18/7/22.
2. NICE: TA728 Midostaurin for treating advanced systemic mastocytosis. Published date: 22nd Sep 2021

Circulation/Dissemination

Date added into Q-Pulse	23rd January 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
August 2022	1.0	Aileen McCaughey Advanced Pharmacist Haemato-Oncology- NMP	V1.0 New Regimen Protocol