Indication	For the treatment of aggressive systemic mastocytosis or aggressive systemic mastocytosis with an associated haematological neoplasm or mast cell leukaemia.
Treatment Intent	Disease modification
Frequency and number of cycles	Repeat every 28 days. Until disease progression or excessive toxicity or patient choice to discontinue. A formal medical review as to whether treatment with avapritinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • **ECG** baseline. • Before initiating treatment with avapritinib the risk of intracranial haemorrhage should be carefully considered in patients with relevant risk factors such as severe thrombocytopenia, vascular aneurysm and a history of intracranial haemorrhage, stroke or TIA. • **Haematological parameters:** • Platelet count should be >/= 50 x 10^9/L for avapritinib treatment. • FBC, U&Es and LFTs every 2 weeks for the first 8 weeks of treatment, then 2-weekly if the platelet count is <75 x 10^9/L, 4-weekly if the platelet count is 75-100 x 10^9/L and then every 3 months if the platelet count is >100 x 10^9/L or as clinically indicated. • **Hepatic impairment:** No dose adjustment is recommended for patients with mild or moderate hepatic impairment. A reduced starting dose of 100mg OD is recommended in severe impairment (Child-Pugh C). • **Renal impairment:** No dose adjustment is required in patients with mild to moderate renal impairment (CrCl 30-89ml/min). No data available in severe impairment or end stage renal disease, not recommended. • **Management of adverse reactions and dose adjustments:** • Interruption of treatment or dose reduction may be required to manage adverse reactions, see table 1 and table 2. • **Intercranial haemorrhages:** Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, or focal weakness) during treatment with avapritinib should interrupt treatment and inform their healthcare professional immediately. Brain imaging by magnetic resonance imaging (MRI) or computed tomography (CT) may be performed at the discretion of the physician based on severity and the clinical presentation. For patients with observed intracranial haemorrhage during treatment with avapritinib, regardless of severity grade, avapritinib should be permanently discontinued. • **Cognitive effects:** Patients should be monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, or difficulty with cognitive functioning. Patients should notify their healthcare professional immediately if they experience new or worsening cognitive symptoms. For patients with observed cognitive effects related to treatment with avapritinib, the recommended dose modification in Table 2 should be followed. • **Fluid retention:** Occurrences of fluid retention, including severe cases of localised oedema, generalised oedema and ascites, have been reported. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention should be carefully investigated and appropriate supportive care and therapeutic measures undertaken.

	• **Gastrointestinal disorders:** Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrheal, or antacid properties. The hydration status of patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice. • **QT interval prolongation:** Avapritinib should be used with caution in patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products that can prolong QT interval such as amiodarone, citalopram, escitalopram, ondansetron; pre-existing cardiac disease; and/or electrolyte disturbances). QT assessment by ECG during treatment should be considered in at-risk patients if clinically indicated. • **Sun exposure:** Patients should be advised to avoid direct exposure to sunlight or minimise exposure. Patients should a high factor sun screen and wear protective clothing. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** • Concomitant use with strong or moderate CYP3A inhibitors (e.g. ketoconazole, itraconazole, posaconazole, voriconazole; certain macrolides such as erythromycin, clarithromycin and telithromycin and grapefruit and grapefruit juice) should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the **starting dose** of avapritinib must be reduced from **200mg** to **50mg** orally once daily. • Co-administration with strong and moderate CYP3A inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital, primidone and St Johns wort) should be avoided. • If co-administration of avapritinib with narrow therapeutic index CYP3A substrates (e.g. alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, sirolimus, tacrolimus) and with medicinal products that can increase the risk of QT prolongation (e.g. amiodarone, citalopram, escitalopram, ondansetron) close monitoring is recommended as plasma concentrations may be altered. • **Missed dose:** If a patient misses a dose of avapritinib, advise them to take the missed dose as soon as possible, provided there are more than 8 hours remaining before the next scheduled dose. If less than 8 hours remain before the next dose, the missed dose should be omitted. The patient should then resume their regular dosing schedule without doubling up or taking two doses within an 8-hour window. If vomiting occurs after taking a dose of avapritinib, the patient should not take an additional dose but continue with the next scheduled dose. • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet. • **Driving:** Avapritinib may cause adverse reactions such as cognitive effects that may influence the ability to drive and use machines. Patients who experience these adverse effects should take special care when driving a car or operating machinery.
References	Blueteq accessed online 06.12.2024 CDF list accessed online 29.12.2024 SPC accessed online 6.12.2024

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

Table 1 Recommended dose reduction for adverse reactions

Dose reduction	**Starting dose 200mg**
First	100 mg once daily
Second	50 mg once daily
Third	25 mg once daily

Table 2 Recommended dose modification for adverse reactions

Adverse reaction	**Severity***	**Dose modification**
Intracranial haemorrhage	All Grades	Permanently discontinue.
Cognitive effects**	Grade 1	Continue at the same dose, reduce dose or interrupt until improvement to baseline or resolution. Resume at the same dose or at a reduced dose.
	Grade 2 or Grade 3	Interrupt therapy until improved to baseline, Grade 1, or resolution. Resume at the same dose or at a reduced dose.
	Grade 4	Permanently discontinue.
Other	Grade 3 or Grade 4	Interrupt therapy until less than or equal to Grade 2. Resume at the same dose or at a reduced dose, if warranted.
Thrombocytopenia	Less than 50 x 10^9/L	Interrupt dosing until platelet count is >/=50 x 10^9/L, then resume at reduced dose (see Table 1). If platelet count does not recover above 50 x 10^9/L, consider platelet support.

* The severity of adverse reactions graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and 5.0

** Adverse reactions with impact on Activities of Daily Living (ADLs) for Grade 2 or higher adverse reactions

Repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**AVAPRITINIB**	**200mg**	PO	OD continuously. Take on an empty stomach, at least 1 hour before or at least 2 hours after a meal. Swallow whole. Available as 25mg, 50mg, 100mg, 200mg and 300mg tablets.
	Metoclopramide	10mg	PO	up to 3 times a day as required. Do not take for more than 5 days continuously.
	Loperamide	2mg-4mg	PO	Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if required.