Avapritinib Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy	C96 C94	00937	N/A

* This applies to post 2012 indications

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Avapritinib is to be taken orally once daily and treatment should be taken continuously.

Cycle frequency and duration:

Each cycle is 28 days. Treatment should continue until disease progression or unacceptable toxicity.

Drug	Dose	Route	Cycle
Avapritinib	200mg once daily[a,b,c,d,e,f]	PO	Continuous
[a]200 mg is the maximum recommended dose of avapritinib for the above indication and must not be exceeded.			
[b]Concomitant use of avapritinib with strong or moderate CYP3A inhibitors should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must be reduced from 200 mg to 50 mg orally once daily			
[c]Avapritinib should be taken on an empty stomach, at least 1 hour before or at least 2 hours after a meal. Patients must swallow the tablets whole with a glass of water.			
[d] If a dose of avapritinib is missed, the patient should make up for the missed dose unless the next scheduled dose is within 8 hours. If the dose has not been taken at least 8 hours prior to the next dose, then that dose must be omitted and the patient should resume treatment with the next scheduled dose.			
[e]If vomiting occurs after taking a dose of avapritinib, the patient must not take an additional dose but continue with the next scheduled dose.			
[f]Avapritinib is commonly available as 25mg, 50mg,100mg and 200mg tablets for this indication			

ELIGIBILITY:

- Indication as above
- ECOG 0-3

CAUTIONS:

- Avapritinib should be used with caution in patients with known QT interval prolongation or at risk of QT interval prolongation for example due to
  - concomitant medicinal products
  - preexisting cardiac disease and/or electrolyte disturbances

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- History of vascular aneurysm, intracranial haemorrhage, cerebrovascular accident within the prior year, concomitant use of anticoagulants or thrombocytopenia.

EXCLUSIONS:

- Hypersensitivity to avapritinib or any of the excipients
- Platelet count < 50 x 10^9/L
- Concomitant use with strong or moderate CYP3A inhibitors or inducers
    - If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib should be reduced from 200 mg to 50 mg orally once daily for patients with Advanced systemic mastocytosis (AdvSM)
- Pregnancy and in women of childbearing potential not using contraception
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal profile and liver profile (bilirubin and transaminases)
- Lactate dehydrogenase (LDH)
- Tryptase
- Electrocardiogram (ECG)
- Coagulation profile: APTT, PT, fibrinogen level
- Pregnancy test

Regular tests:

- FBC, renal profile and liver profile (bilirubin and transaminases)
- Platelets every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks, monitor platelet counts as follows:
    - every 2 weeks (or more frequently as clinically indicated) if values are less than 75 x 10^9/L,
    - every 4 weeks if values are between 75 and 100 x 10^9/L
    - as clinically indicated if values are greater than 100 x 10^9/L
- LDH
- Tryptase
- Coagulation profile: APTT, PT, fibrinogen level
- ECG as clinically indicated
    - Interval assessments of QT by ECG should be considered if avapritinib is taken concurrently with medicinal products that can prolong QT interval
- Monitor for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, and/or difficulty with cognitive functioning
- Routine surveillance of haemorrhagic adverse reactions such as intracranial haemorrhage
- Regular assessment of weight and fluid overload

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Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Interruption of treatment with or without dose reduction may be considered to manage adverse reactions based on severity and clinical presentation. The dose should be adjusted as recommended, based on safety and tolerability
- Dose reductions and modifications for the management of adverse reactions are provided in Tables 1, 2 and 3 below

Table 1. Recommended dose reductions for avapritinib for adverse reactions

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

Renal and Hepatic Impairment:

Table 2: Dose modification of avapritinib in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
CrCl (mL/min)	**Dose**	**Severity**	**Dose**
≥ 30	No dose adjustment is needed	Mild and moderate	No dose adjustment is needed
< 30	No need for dose adjustment is expected	Severe	Not recommended However, the SmPC recommends a modified starting dose of 100mg PO OD for patients with severe hepatic impairment (Child-Pugh Class C).
Haemodialysis	No need for dose adjustment is expected		
Recommendations as per Giraud et al 2023. Additional information on starting dose in patients with hepatic impairment Child-Pugh Class C from SmPC			

Management of adverse events:

Table 3. Recommended dose modifications for avapritinib for adverse reactions

Adverse reaction	Severity*	Dose Modification
Intracranial haemorrhage	All Grades	Permanently discontinue avapritinib
Cognitive effect**	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 avapritinib
Other adverse reactions	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.

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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.
* Severity 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		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

Avapritinib: Moderate to high **(Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

- Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy
- Women of childbearing potential should use effective contraception during treatment and for 6 weeks after the last dose of avapritinib. Males with female partners of childbearing potential must use effective contraception during treatment and for 2 weeks after the last dose of avapritinib
- Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with avapritinib. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF)

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for full details of adverse effects.
- Please note the NCCP National SACT regimens do not provide information regarding black triangle (▼) status. Please refer to the relevant Summary of Product Characteristics (SmPC) for this information

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REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Haemorrhages**: Avapritinib has been associated with an increased incidence of haemorrhagic adverse reactions, including serious and severe adverse reactions, like gastrointestinal haemorrhage and intracranial haemorrhage, in patients with advanced systemic mastocytosis (AdvSM). Routine surveillance of haemorrhagic adverse reactions in patients with AdvSM must include physical examination. Complete blood counts, including platelets, and coagulation parameters must be monitored in patients with AdvSM, particularly in patients with conditions predisposing to bleeding, and in those treated with anticoagulants (e.g. warfarin and phenprocoumon) or other concomitant medicinal products that increase the risk of bleeding.
- **Intracranial haemorrhages:** Adverse reactions of intracranial haemorrhage occurred in AdvSM patients who received avapritinib. Before initiating avapritinib at any dose the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with a history of vascular aneurysm, intracranial haemorrhage, cerebrovascular accident within the prior year, concomitant use of anticoagulants or thrombocytopenia. Patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, and/or focal weakness) during treatment with avapritinib must interrupt dosing of avapritinib 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 in any indication, regardless of severity grade, avapritinib must be permanently discontinued. Serious adverse reactions of intracranial haemorrhage were reported in patients with AdvSM receiving avapritinib. The exact mechanism is unknown. The incidence of intracranial haemorrhage was higher in patients with platelet counts <50 x 10^9 /L and in patients with a starting dose of ≥300 mg. Considering the above, a platelet count must be performed prior to initiating therapy. Avapritinib is not recommended in patients with platelet counts <50 x 10^9 /L.
- **Cognitive effects:** Cognitive effects such as memory impairment, cognitive disorder, confusional state, and encephalopathy, can occur in patients receiving avapritinib. The mechanism of the cognitive effects is not known. It is recommended that patients with AdvSM are clinically monitored for signs and symptoms of cognitive events such as new or increased forgetfulness, confusion, and/or difficulty with cognitive functioning. Patients with AdvSM must notify their healthcare professional immediately if they experience new or worsening cognitive symptoms. For AdvSM patients with observed cognitive effects related to treatment with avapritinib, the recommended dose modification in Table 3 must be followed. In clinical studies conducted in patients with AdvSM, dose reductions or interruptions improved Grade ≥2 cognitive effects compared to no action.
- **Fluid retention:** In patients with AdvSM, localised (facial, periorbital, peripheral, pulmonary oedema, pericardial and/or pleural effusion) or generalised oedema, and ascites have been observed with a frequency category of at least common. Other localised oedemas (laryngeal oedema) have been reported uncommonly. Therefore, it is recommended that patients with AdvSM be evaluated for these adverse reactions including regular assessment of weight and respiratory symptoms. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention must be carefully investigated and appropriate supportive care and therapeutic measures, such as diuretics, should be

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undertaken. For AdvSM patients presenting with ascites, it is recommended to evaluate the aetiology of ascites.

- **QT interval prolongation**: has been observed in patients with AdvSM treated with avapritinib in clinical studies. QT interval prolongation may induce an increased risk of ventricular arrhythmias, including Torsade de pointes. Avapritinib should be used with caution in AdvSM patients with known QT interval prolongation or at risk of QT interval prolongation (e.g. due to concomitant medicinal products, preexisting cardiac disease and/or electrolyte disturbances). Concomitant administration with strong or moderate CYP3A4 inhibitors should be avoided due to the increased risk of adverse reactions, including QT prolongation and related arrhythmias. If concomitant use of moderate CYP3A4 inhibitors cannot be avoided the starting dose of avapritinib must be reduced as per treatment table above. In patients with AdvSM, interval assessments of QT by electrocardiogram (ECG) should be considered if avapritinib is taken concurrently with medicinal products that can prolong QT interval.
- **Gastrointestinal disorders:** Diarrhoea, nausea and vomiting were the most commonly reported gastrointestinal adverse reactions in patients with AdvSM. AdvSM patients who present with diarrhoea, nausea and vomiting should be evaluated to exclude disease -related aetiologies. Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrheal, or antacid properties. The hydration status of AdvSM patients experiencing gastrointestinal adverse reactions must be closely monitored and treated as per standard clinical practice.
- **Photosensitivity reaction:** Exposure to direct sunlight must be avoided or minimised due to the risk of phototoxicity associated with avapritinib. Patients must be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).
- **Effects on ability to drive and use machines:** avapritinib may cause adverse reactions such as cognitive effects that may influence the ability to drive and use machines. Patients should be made aware of the potential for adverse reactions that affect their ability to concentrate and react. Patients who experience these adverse effects must take special care when driving a car or operating machinery.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Gotlib, J., Reiter, A., Radia, D.H. et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med 27, 2192–2199 (2021). https://doi.org/10.1038/s41591-021-01539-8
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. NCCN. Clinical Practice Guidelines in Oncology; Antiemesis. 2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pd
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://assets.hse.ie/media/documents/Classification_Document_for_Systemic_Anti-_Cancer_Therapy_SACT_Induced_Nausea__pWgDCrm.pdf

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5. Herrstedt J et al. 2023 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting. ESMO OPEN Science for Optimal Cancer Care. Volume 9 Issue 2 102195 February 2024. Available at: https://www.esmoopen.com/article/S2059-7029(23)01436-9/fulltext
6. Avapritinib (AYVAKYT®) tablets Summary of product characteristics. Accessed March 2026. Last updated 09/01/2026.Available at: https://www.ema.europa.eu/en/documents/product-information/ayvakyt-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	15/05/2026		Dr Claire Andrews

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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