NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using avapritinib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: May 2026

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using avapritinib in the NHS in England.

For further details, see NICE's technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 18 June 2026
- Second evaluation committee meeting: To be confirmed
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Avapritinib should not be used to treat moderate to severe indolent systemic mastocytosis that is inadequately controlled on symptomatic treatment in adults.

1.2 This recommendation is not intended to affect treatment with avapritinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

These are NICE's draft recommendations. If these recommendations become final, avapritinib would not be required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because there is not enough evidence to suggest avapritinib offers value for money in this population.

Why the committee made these recommendations

Standard treatment for moderate to severe indolent systemic mastocytosis is symptomatic treatment (also called symptom-directed therapy). This aims to manage symptoms. Avapritinib aims to treat the underlying condition.

Clinical trial evidence shows that avapritinib reduces the severity of symptoms compared with symptom-directed therapy alone.

There are uncertainties in the economic model. It is unclear if the population and

definition of treatment response used in the model are the same as in NHS practice. And there are uncertainties about some of the assumptions, including that the modelling:

- did not account for people having a higher dose of avapritinib in the trial
- did not fully account for missing data on quality of life
- did not use evidence to estimate the differences in costs when there was a response to treatment.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for avapritinib. So, avapritinib should not be used.

2 Information about avapritinib

Marketing authorisation indication

2.1 Avapritinib (Ayvakyt, Blueprint Medicines) is indicated for 'the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for avapritinib.

Price

2.3 £26,667.00 for a 30-pack of 25 mg tablets (excluding VAT; BNF online accessed May 2026).

2.4 The company has a commercial arrangement. This makes avapritinib available to the NHS with a discount and it would have also applied to this indication if avapritinib had been recommended. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Blueprint Medicines will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Blueprint Medicines, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Systemic mastocytosis is caused by an excess number of mast cells gathering in the body's tissues, which affects the skin, internal organs and bones. It can be categorised into 3 subtypes (indolent, smouldering, or advanced) using a clinical classification system from the World Health Organization. Indolent systemic mastocytosis (ISM) is the most common subtype. Symptoms can include rashes, itchy skin, diarrhoea, nausea, issues with cognition, fainting, high heart rate, organ dysfunction and anaphylaxis. But the clinical and patient experts explained that people with ISM have individual symptom profiles that can be very different from each other. Most symptoms of ISM happen during 'flare-ups' when mast cells become activated. The patient and clinical experts explained that triggers for flare-ups are very variable, and individual for each patient. They include normal daily activities such as walking, heat from the sun, or mild stress related to everyday life (for example, opening an email). The patient experts explained that the unpredictability of flare-ups and the many possible triggers mean people with ISM often have to build their life around potential triggers. They explained that living with ISM makes it difficult to hold employment, and causes anxiety about the impact the condition has on people close to them. The committee concluded that ISM significantly impacts quality of life.

Clinical management

Moderate to severe ISM

3.2 The marketing authorisation for avapritinib is in moderate to severe ISM. The clinical experts noted there is no definitive method of classification by symptom severity. But it will be decided by clinician opinion and may include a symptom rating system. The company developed a proprietary symptom-rating system for ISM called the ISM-SAF. This is a patient-reported measure that asks people to rate the severity from 0 to 10 of 11 potential symptoms across 3 domains of ISM (gastrointestinal, skin and neurocognitive symptoms). It produces a total symptom score (TSS) ranging from 0 to 110. Using the ISM-SAF TSS, the company categorise people with ISM as having mild symptoms (TSS of less than 28) and moderate or severe symptoms (TSS of 28 or more). The higher the score the more severe the symptoms. The EAG was advised that the ISM-SAF is not used in all treatment centres in the NHS, which may mean that the population of the appraisal is not fully representative of the NHS population who would be eligible for avapritinib (see section 3.4 and section 3.6). The clinical experts confirmed that the ISM-SAF is not routinely used in clinical practice. They noted that the company intends to make the tool non-proprietary and available to all centres. The clinical experts stated they would welcome the use of a tool in clinical practice to determine severity of the condition. They noted the tool is quick to fill out and clinicians are used to using scoring systems for other disease areas. The company defined the moderate to severe population in this appraisal as having an ISM-SAF TSS of 28 or greater. But the clinical experts stated that they would also use clinical judgement, rather than just base treatment decisions on meeting a certain score; for example, when assessing people who have 1 or 2 severe symptoms but have a TSS lower than 28. The committee was concerned that the NHS would offer treatment to a wider group of people than that defined by the company as having moderate to severe disease. But the clinical experts explained that

the number of people who would be classed as having mild disease with 1 or 2 severe symptoms is small. Also, when deciding whether to have treatment, the individual would need to weigh up the impact of that symptom with the potential side-effects of the treatment. The committee concluded that ISM-SAF-TSS is a suitable measure to define the moderate to severe ISM population in the NHS. But if clinical judgement is also going to be used to assess eligibility for treatment, the committee wanted to account for this in the economic model (see section 3.6).

Comparators

3.3 There are no disease-modifying treatments available for ISM. Current standard of care is symptom-directed therapy (SDT), which aims to prevent and treat symptoms based on a person's individual symptom profile. The clinical and patient experts explained that this means people with ISM often need a large number of regularly-used medications, which can be difficult to manage for both people with ISM and their healthcare professionals. They also noted that current treatments have been unchanged in many years and are not considered to be very effective. For people with inadequately controlled moderate to severe ISM, some immune system modifying treatments may be used. These include interferon-alpha and omalizumab. The company also included off-label tyrosine kinase inhibitors in its treatment pathway for SDT and in its model for the SDT-alone arm. It stated that it included these because of evidence suggesting that tyrosine kinase inhibitors are used in a small subgroup of people with ISM. The clinical experts advised that tyrosine kinase inhibitors are not reimbursed and are not used in the NHS for this condition. The committee concluded that people with ISM and their healthcare professionals would welcome a new treatment option for ISM. The committee also concluded that tyrosine kinase inhibitors are not a relevant treatment in the NHS and should not be included in the SDT-alone arm of the company's model.

Clinical effectiveness

PIONEER

3.4 Clinical evidence for avapritinib came from PIONEER. This was a phase 2 randomised controlled trial comparing the effectiveness of avapritinib plus SDT with placebo plus SDT. It was separated into 3 parts. The first part established the optimal dosing for avapritinib for treating ISM. The second part was the main assessment of clinical effectiveness across 24 weeks. The third part is an ongoing open-label extension. The population of PIONEER was people with a confirmed diagnosis of ISM using World Health Organization criteria and with an ISM-SAF-TSS of 28 or higher. The primary outcome of part 2 of PIONEER was mean change in ISM-SAF-TSS from baseline to week 24. The avapritinib arm showed an average change from baseline TSS of −15.58 points, compared with −9.15 in the placebo arm. This showed a statistically significant difference between groups of −6.43 points (95% confidence interval −10.90 to −1.96, p=0.003). The EAG noted that although the overall results showed a strong improvement in TSS, the response was variable across the different symptom domains measured by the ISM-SAF. Symptoms in the skin symptom domain showed the strongest improvements for the avapritinib arm compared with placebo (group difference −3.23, p<0.0001). Symptoms in the gastrointestinal symptom domain (group difference −0.60, p=0.410) and the neurocognitive symptom domain (group difference −1.22, p=0.102) showed smaller improvements compared with placebo, and were not statistically significant. The committee was concerned about the variability of the treatment effect across symptom domains, especially considering the potential restriction of avapritinib to moderate and severe ISM defined using the TSS (see section 3.2 and section 3.6). The committee agreed that the evidence showed avapritinib was effective in reducing overall symptom severity, but it was concerned about the variability across symptom domains. So it

requested the company provide further evidence, if available, on the effect of avapritinib by symptom domain.

Generalisability of PIONEER

3.5 The EAG raised concerns around the generalisability of the trial to NHS practice. These included the use of ISM-SAF-TSS as an eligibility criterion, because not all NHS centres are using the tool (see section 3.2). The EAG also raised concerns that dose escalation from 25 mg to 50 mg was permitted in part 3 of PIONEER, despite it being expressly forbidden by the marketing authorisation (see section 2.2). The EAG also raised concerns that some treatments included in SDT as part of the trial, especially omalizumab, appeared to differ from the company's and the EAG's clinical expert estimations of their use in the NHS. The clinical experts at the meeting agreed that the use of omalizumab in PIONEER appeared higher than they would expect in clinical practice, but the nature of SDT means the use of omalizumab would be expected to be variable depending on the symptom profile of the selected population. The clinical experts also noted that omalizumab may not be available in all centres at all times. The committee acknowledged the difference in omalizumab use between the trial and NHS practice, but decided that SDT as used in the trial was sufficient for decision making. The committee was concerned about the impact that dose escalation may have had on the generalisability of the long-term results of PIONEER to NHS practice. But it concluded that PIONEER was suitable for decision-making, if proper adjustments for dose escalation are made (see section 3.7).

Economic model

Company's modelling approach

3.6 To compare avapritinib 25 mg with SDT in people with moderate to severe ISM the company presented a disease activity model. It used TSS to derive health states based on mild, moderate and severe symptom groups. The model structure included an initial treatment period and then

separated 'responders' and 'non-responders' at 24 weeks. The EAG found the symptom-based structure of the model to be suitable in concept. But it raised issues about the generalisability of the model structure to NHS practice, including:

- the use of the ISM-SAF-TSS for classifying symptom severity is not used in all centres in the UK, and may exclude some people likely to have avapritinib in the NHS (see sections 3.2 and 3.5)
- tyrosine kinase inhibitors were included in the company's modelled SDT, despite the lack of reimbursement in the NHS (see section 3.3)
- the mean starting age in the model was 40 years, but the mean starting age in PIONEER was 51. The EAG's clinical expert advised the average age in their practice is about 51. So, the EAG preferred to use 51 as the starting age in its base case.

The clinical experts at the meeting advised that the average age in their practice is about 40 to 45 years. The committee considered the generalisability of the model structure. It agreed with the EAG that there are several areas of uncertainty about the model structure. It noted that to adequately capture the heterogeneity of the disease a patient simulation model would have been a more methodologically appropriate approach. It requested that the company update the model to address the uncertainty identified by the EAG, but accepted the company's overall model structure as appropriate for decision making. The committee requested the following changes:

- removing tyrosine kinase inhibitors from the modelled SDT treatments
- doing sensitivity analysis around the eligibility criteria for avapritinib; for example, providing scenarios that include people with a mild TSS, who have severe symptoms in 1 or 2 domains, if evidence is available
- providing robust evidence about the average age of people with ISM in NHS practice

- doing scenario analyses to consider the impact of starting age on the model results.

Dose escalation

3.7 The population in the company model included people with moderate and severe ISM who had not had a dose escalation in PIONEER from 25 mg to 50 mg. The company said this was to align with the UK marketing authorisation of avapritinib for ISM, which states that escalation to higher doses is not permitted. The company noted that dose escalation to 50 mg in PIONEER part 3 was a protocol-defined option and was not implemented as a routine escalation for patients who did not have a treatment response. It was permitted only for patients who previously had demonstrated benefit and tolerability on avapritinib and subsequently experienced worsening of symptoms after entering part 3 of PIONEER. The EAG noted that the results for people who dose escalated were similar to those who did not, but it was unclear if the results would be the same without the escalation. It noted that only people without response on 25 mg avapritinib would escalate their dose to 50 mg. The EAG advised this meant that a significant proportion of people who did not respond to the licensed 25 mg were removed from the analysis. The EAG suggested a simple conservative analysis to account for dose escalation would be to assume everyone who had an escalated dose is modelled as non-responders, because only people who did not have a response to treatment at the 25 mg dose would be likely to escalate to 50 mg. Another method would be to do a formal crossover adjustment, if the evidence was available for such an approach. The committee was concerned that by removing people who had escalated their dose from the model, there may be bias in the modelled treatment effect of avapritinib (only those for whom the treatment was working are modelled and those who are not responding are removed). It agreed with the EAG that some adjustment should be made to account for people who escalated their dose of avapritinib, while only considering the efficacy of the licensed 25 mg dose.

The committee concluded that the company should explore options for including people who escalated their dose; for example, by doing an analysis that assumes everyone who escalated their dose are non-responders, or a formal crossover adjustment analysis if the evidence allows.

Duration of treatment

Stopping treatment at 24 weeks for non-response

3.8 The company included a 24-week stopping rule for non-responders in the modelling. Non-response was defined as less than a 30% reduction in TSS and response was defined as 30% or more reduction in TSS, assessed at 24 weeks. This was based on the expectation that treatment effect will be regularly assessed in practice and treatment will be stopped if response is not present. It considered 24 weeks to be clinically reasonable and appropriate, and said this was confirmed by clinical experts. The EAG was concerned that this was not in line with the evidence from the trial or the marketing authorisation. The EAG noted that the modelled proportion of people having avapritinib at week 24 was significantly lower than at the same time point in PIONEER (both the observed proportion from PIONEER and the modelled proportion of people remaining on treatment with avapritinib at week 24 are considered confidential by the company, so cannot be reported here). The EAG preferred to remove the stopping rule for non-response from its base case. The clinical experts advised that assessing response to treatment is common in NHS practice in other disease areas, and that 24 weeks was a reasonable timepoint to choose. The clinical experts estimated that about 60% to 70% of people who had avapritinib in the NHS would respond by week 24, which is higher than the modelled proportion but lower than the proportion observed in PIONEER. The company emphasised that some people in PIONEER continued to have avapritinib despite not reaching the response threshold. The clinical experts advised that although a reduction

of 30% or more in TSS was a reasonable threshold for response, clinical judgement would also be used. This includes if someone had a score close to the threshold, if they had a strong response in 1 domain but not others, or they responded in a way that would not be captured by the ISM-SAF. But the clinical experts also noted that the side-effects of avapritinib mean that people would be unlikely to continue treatment with avapritinib if it was not effective. The committee considered the use of a stopping rule for non-response at 24 weeks. It was concerned that stopping treatment after no response at 24 weeks was outside of the trial and marketing authorisation. Also, it was concerned about the self-reporting nature of the TSS score and that a cut-off of 30% does not allow clinical judgement if someone has a score that does not meet the cut-off but they are benefiting from treatment. So, the committee concluded it was uncertain about the stopping rule and would consider the revised modelling with and without the stopping rule. It also requested 2 further scenarios with the stopping rule assuming:

- 60% to 70% of people having avapritinib continue having it after 24 weeks
- treatment is only stopped at 24 weeks if there has been no reduction in TSS score; people who still have a response continue having treatment, even if the reduction in TSS is less than 30%.

Long-term treatment discontinuation

3.9 The company stated the long-term data from PIONEER was not mature enough to reliably extrapolate the maximum treatment duration of avapritinib. So, it used real-world evidence from a patient assistance programme in the US. The company extrapolated the Kaplan–Meier data from the US real-world evidence. It derived the maximum treatment duration by taking the mean of all the mean extrapolated times on treatment, after excluding the Gompertz and generalised gamma extrapolations because they were deemed clinically implausible. The EAG

advised that because the maximum treatment duration was derived from mean extrapolated treatment duration of the US real-world evidence, it likely underestimates the true maximum treatment duration. The EAG was also concerned that the maximum treatment duration may double-count discontinuation events from lack of response and adverse events. The EAG was not convinced that the US real-world evidence was a more suitable source for treatment discontinuation than the long-term data from PIONEER. The committee decided that the long-term data from PIONEER is more representative of treatment discontinuation in NHS practice than the real-world evidence from the US. This is because the trial included UK sites, is the data source used for the efficacy of avapritinib, and the clinical experts advised the trial data on long-term treatment discontinuation is a reasonable source of evidence. So, the committee concluded that the company should provide analysis using treatment-duration data from PIONEER.

Disease progression in the model

Use of trial data to inform transitions in the model

3.10 To model progression between ISM health states the company directly took health-state data from the trial, rather than using derived transition probabilities. The EAG noted this may result in overfitting of the data. The company justified its approach by explaining that treatment effects occur early, at about 3 to 6 months, and then stabilise. The company noted that this makes transition probabilities small and hard to estimate reliably. To limit overfitting, it chose a minimum of 10 people to inform the distribution. The EAG preferred to use a minimum of 20 people to inform the distribution, to stabilise the results at later timepoints. The committee decided that deriving transition probabilities from the trial data, rather than directly using health states from the trial, would provide a more reliable representation of disease progression. So, it concluded that the company should use transition probabilities in its model.

Disease progression in the SDT arm

3.11 The company's model assumed that people in the SDT-only arm would return to their baseline symptom score after the end of the trial period (24 weeks). But people in the avapritinib arm continued in their last observed health state. It justified this assumption based on advice from clinical experts that SDT provides symptom control only and is not disease modifying. So, the company assumed there is no sustained improvement. The EAG raised several concerns about the company's approach. It noted that even though SDT is not symptom-modifying, controlling symptoms would likely have a positive effect on quality of life in the long term. This is not currently captured in the company's model. Also, there was no evidence that symptoms return to baseline at the end of the SDT follow-up period in PIONEER (24 weeks). Instead, the percentage of patients with response continued to increase up to 24 weeks. So, the EAG preferred to have people in the SDT-only arm remain in their last observed health state. The clinical experts advised there would likely be some return to baseline symptoms after trial conditions were removed. The committee was concerned with the company's approach to modelling disease progression in the SDT arm. It noted that a response was observed in both arms of the trial up to 24 weeks. Removing this response in the SDT arm of the model could bias comparisons between treatment arms, because people in the avapritinib arm would also be expected to respond better under trial conditions. The committee concluded that people in the SDT-only arm should remain in their last observed health state after 24 weeks in line with the modelling for the avapritinib arm.

Progression to advanced-disease health states

3.12 The company modelled a transition to smouldering systemic mastocytosis and advanced systemic mastocytosis. It applied a higher probability for transition to these health states for people categorised as having severe symptoms. To justify this assumption, the company cited a study by Matito et al. (2013). This showed a higher risk of progression to more advanced

systemic mastocytosis states in people with higher serum tryptase levels. The company stated this suggests that progression to the more advanced states would also be linked to more severe symptoms. The EAG advised that Matito et al. (2013) only referred to serum tryptase, and there was no evidence of a link between ISM-SAF-TSS (which defined the severe health state) and progression to more advanced forms of systemic mastocytosis. It found several programming errors in the company's modelling of progression, including in progression to more advanced systemic mastocytosis states. It advised that this resulted in a mortality benefit for avapritinib, despite the company making an explicit modelling assumption that avapritinib would have no mortality benefit. The EAG was unable to fix the errors, so it preferred to remove progression to more advanced systemic mastocytosis states from its base case. The clinical experts agreed with the EAG that there was no evidence of a link between ISM-SAF-TSS and progression to more advanced forms of systemic mastocytosis. The committee agreed there was no evidence indicating a relationship between severity of ISM and progression to more advanced forms of systemic mastocytosis. It recognised that errors in the company's model meant that progression to these health states was not being accurately represented. So, it requested that the company fix these errors, and then use the same risk of progression to more advanced forms of systemic mastocytosis for all ISM health states.

Utility values

3.13 The company derived utility values for each health state using data from PIONEER. To account for missing data, it used the last observation carried forward method in its base case. The EAG advised that using mixed models for repeated measures was more suitable to adjust for the missing data. It suggested that multiple imputation may also be suitable. The company indicated in the committee meeting that it had now done a mixed model for repeated measures, which it would provide to the committee at the next meeting. The company also modelled a utility

benefit for people in the avapritinib arm who had a response to treatment but remained in the severe health state. It stated that this was because a 30% or more reduction in TSS was a clinically meaningful benefit that would otherwise not be captured in the modelling. The EAG noted that applying the benefit would likely result in double counting, because the utility estimate from PIONEER for the severe health state already included a mix of responders and non-responders. So, the EAG removed the benefit from its base case. The committee agreed with the EAG that the last observation carried forward was not a suitable method for adjusting for missing data in this case. It agreed that a mixed models for repeated measures analysis was more appropriate. The committee also requested that the company provide a more systematic method to derive and describe utility values for each health state. This should include a stepwise selection model to identify variables, consideration of whether health state is predictive of utility benefit, and analysis using multiple imputation to adjust for missing utility data.

Costs

Resource use

3.14 The company modelled different resource-use costs for each health state, with lower costs for responders in each health state. To derive the costs for each health state, the company consulted a Dutch advisory board and did a survey of UK clinicians. It decided to use the costs obtained from the Dutch advisory board, which it said were the most conservative. The EAG advised that the Dutch advisory board costs were not the most conservative in all areas (for example, costs relating to the neurological symptom domain and blood monitoring costs). It recommended exploration of the costs suggested by UK clinicians. The EAG noted that the Dutch advisory board experts differentiated responders compared with non-responders, not by health states. But the model applies costs by both response status and health state, and it is unclear how the inputs were

combined. There was also uncertainty about whether experts knew a responder benefit was added on top of health-state effects. The EAG also noted that the model applies reduced resource use (responder benefit) to all patients having avapritinib after 1 year, but this is only appropriate if non-responders stop treatment. When stopping rules are not used (as in the EAG's base case) all people in the avapritinib arm have this benefit, which may be unrealistic. The EAG explored a scenario removing the responder-related cost benefit. The committee noted that the EAG's scenario had a very large impact on the incremental cost-effectiveness ratio (ICER). The committee decided that the current model is unlikely to have properly captured the true impact of reduced resource use for avapritinib. The committee agreed that UK data should be more thoroughly explored, and requested the company provide further justification for its choice of source of resource use. The committee also requested that the company provide more evidence for the size of the reduction in resource use for responders.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.15 The company's and EAG's base cases differed, because of the following assumptions:

- the mean starting age in the model (see section 3.6)
- the inclusion of tyrosine kinase inhibitors as an SDT treatment (see section 3.6)
- the inclusion of the 24-week response checkpoint (see section 3.8)
- the minimum amount of people required to derive health-state distribution in the model (see section 3.10)
- the health state of people in the SDT-only arm after 24 weeks (see section 3.11)
- the inclusion of progression to more advanced systemic mastocytosis states (because of errors in the modelling, see section 3.12)

- the inclusion of a utility benefit for avapritinib responders (see section 3.13).

The company's and EAG's base cases were both significantly above £35,000 per quality-adjusted life year (QALY) gained when compared with SDT alone (the exact ICERs are confidential because of confidential prices for other treatments). The EAG's scenario that removed the responder-related cost benefit increased the ICER substantially (see section 3.14).

Acceptable ICER

3.16 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- the treatment effect of avapritinib appeared to vary across symptom domains (see section 3.4)
- the population that would have avapritinib in clinical practice may differ from the modelled population (see section 3.6)
- people who escalated their dose in part 3 of PIONEER were excluded from the analysis used in the model (see section 3.7)
- the response threshold for stopping treatment in the model may not align with what would happen in clinical practice (see section 3.8)
- the maximum treatment duration applied in the model was derived from the average extrapolated treatment duration from US real-world evidence (see section 3.9)

- missing utility data was not appropriately handled (see section 3.13)
- the size of the cost reduction for responders was not evidence based (see section 3.14).

The committee agreed that it could not conclude on an acceptable ICER before its concerns about the evidence had been addressed.

Committee's preferred assumptions

3.17 The committee noted that, before it could establish a plausible cost-effectiveness estimate for avapritinib, more evidence and analysis is needed. It asked the company to provide the following:

- further evidence, if available, on effects of avapritinib by symptom domain (see section 3.4)
- modelling of SDT treatments without tyrosine kinase inhibitors (see section 3.6)
- evidence about the average age of people with ISM in NHS practice and scenario analyses to show the impact of different starting ages in the model (see section 3.6)
- sensitivity analysis around the TSS threshold used to define eligibility for avapritinib (see section 3.6)
- analysis accounting for people who escalated their dose of avapritinib in part 3 of PIONEER, adjusted to consider evidence relating only to the licensed 25 mg dose (see section 3.7)
- scenario analysis with and without a stopping rule (see section 3.8)
- sensitivity analysis around the TSS threshold used to define response in the model (see section 3.8)
- analysis of maximum treatment duration using long-term data from PIONEER (see section 3.9)
- analysis using derived transition probabilities (see section 3.10)
- modelling that people in the SDT arm carry forward their last observed health state after 24 weeks (see section 3.11)

- modelling the same risk of progression to more advanced forms of systemic mastocytosis for all ISM health states (see section 3.12)
- correction of programming errors related to progression (see section 3.12)
- a more systematic method to derive and describe utility values for each health state, including a stepwise selection model to identify variables, consideration of whether health state is predictive of utility benefit, and analysis using multiple imputation to adjust for missing utility data (see section 3.13)
- utility values derived from analysis using mixed models for repeated measures or multiple imputation to adjust for missing data (see section 3.13)
- exploration of the UK clinician data on costs (see section 3.14)
- more evidence about the size of the reduction in resource use for responders (see section 3.14).

Managed access

Recommendation with managed access

3.18 Having concluded that avapritinib could not be recommended for routine use in the NHS, the committee considered if it could be recommended for use during a managed access period. The company did not make a proposal for managed access to be considered. The NHS England Cancer Drugs Fund lead noted that there was medium likelihood that managed access would resolve uncertainties. They noted there may be potential to reduce some uncertainty in the long-term data, for example, around adherence to the stopping rule (see section 3.8) and duration of treatment (see section 3.9). But they noted there were no plausibly cost-effective ICERs. So, the committee concluded that avapritinib did not meet the criteria to be considered for a recommendation with managed access.

Other factors

Equality

3.19 The committee noted concerns from stakeholders that avapritinib cannot be taken during pregnancy. The committee also noted concerns that some current treatments for ISM may contain gelatine, which is not suitable for people from certain religious backgrounds. But the committee noted that the only existing treatment that has no gelatine-free formulation is midostaurin, a tyrosine kinase inhibitor that is not considered a comparator. Pregnancy, religion and belief are protected under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed these were no potential equalities issues.

Uncaptured benefits

3.20 The committee considered whether there were any uncaptured benefits of avapritinib. It noted that modelled resource use had not been properly captured to account for changes in SDT use after response to avapritinib (see section 3.14). It recalled that it had asked the company to capture this as part of modelling changes to resource use. The committee noted there may be an uncaptured benefit from the reduction in numbers of tablets that people need for current treatment options. The committee also acknowledged that avapritinib is the first disease-modifying treatment in this disease. The committee understood from the patient and clinical experts that current treatment options focus on supportive care only, have remained unchanged for many years, and that they would welcome a new disease-modifying treatment. A patient expert noted that the ISM-SAF does not capture anaphylaxis as a symptom, which is a key concern of patients, so this had not been captured in the economic model. The committee acknowledged that changes in frequency of anaphylaxis had not been captured by the modelling and decided this was an important outcome that may result in cost-savings for the healthcare system. The

committee concluded there are several uncaptured benefits that had not been captured by the economic modelling.

Conclusion

Recommendation

3.21 The committee could not choose a preferred ICER because of the substantial uncertainty in the evidence. But there were no plausibly cost-effective ICERs. So, the committee concluded that it could not recommend avapritinib for treating inadequately controlled moderate to severe indolent systemic mastocytosis in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

George Millington
Technical lead

Victoria Kelly
Technical adviser

Kate Moore
Project manager

Ross Dent
Associate director

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