NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Nirogacestat for treating desmoid tumours

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nirogacestat 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using nirogacestat in the NHS in England.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: 1st June 2026
- Second evaluation committee meeting: 17th June 2026
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Nirogacestat should not be used to treat progressing desmoid tumours that need systemic treatment in adults.

1.2 This recommendation is not intended to affect treatment with nirogacestat 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, nirogacestat 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 determine whether nirogacestat is value for money in this population.

Why the committee made these recommendations

Usual treatment for progressing desmoid tumours that need systemic treatment is non-curative and aimed at symptom management. This can include chemotherapy, which is not licensed for treating desmoid tumours.

Clinical trial evidence shows that nirogacestat increases how long people have before their condition gets worse compared with placebo.

Nirogacestat has not been directly compared with chemotherapy in a clinical trial. Indirect comparisons suggest that nirogacestat is likely to work as well as chemotherapy, but this is uncertain.

There are uncertainties with the economic model. This is because of the assumptions made about how nirogacestat affects quality of life.

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

2 Information about nirogacestat

Marketing authorisation indication

2.1 Nirogacestat (Ogsiveo, SpringWorks Therapeutics) is indicated for 'the treatment of adult patients with progressing DT who require systemic treatment'.

Dosage in the marketing authorisation

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

Price

2.3 The anticipated list price is £15,189.04 per 56 pack of 150-mg tablets (company submission).

2.4 The company has a commercial arrangement, which would have applied if nirogacestat had been recommended.

Sustainability

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

3 Committee discussion

The evaluation committee considered evidence submitted by SpringWorks Therapeutics, 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

3.1 Desmoid tumours are a rare type of intermediate, locally aggressive soft tissue tumour. They are often associated with CTNNB1 genetic mutations, but have also been linked to trauma, surgery, hormonal changes and pregnancy, and a small proportion (5% to 10%) are associated with familial adenomatous polyposis (FAP). The clinical experts explained that the condition is highly heterogenous with an unpredictable disease course and appears in various parts of the body, making treatment challenging. Symptoms and prognosis depend on where the tumour is located and how big it is, with some people experiencing no symptoms and others experiencing substantial pain, loss of function and mortality. The patient experts explained that it is difficult to live with desmoid tumours and how the most debilitating symptom is usually pain, but that mobility can also be affected depending on the tumour size and location. They also highlighted the emotional impact, with many people with desmoid tumours experiencing anxiety and depression, as well as desmoid tumours affecting careers, relationships and social lives, and the ability to have a family. The committee acknowledged the significant impact on quality of life that desmoid tumours can have for people living with the condition and their families and carers.

Treatment pathway

3.2 There are no NICE-recommended treatments for desmoid tumours. The initial approach after diagnosis is based on clinical assessment, which includes symptoms, location of the tumour and risk. When tumours are asymptomatic and non-threatening, management consists of active surveillance with monitoring and no immediate treatment. If tumours become symptomatic, progress, or threaten function, active treatment may be indicated. In this setting, treatment is non-curative and aims to control tumour growth and alleviate symptoms rather than address the

underlying cause of the disease. Current treatment options include off-label chemotherapy, tyrosine kinase inhibitors (TKIs) and surgery. The NHS England clinical lead noted that TKIs are not commissioned in the NHS in England for desmoid tumours, so they would only be used through compassionate access or company-sponsored programmes. The clinical and patient experts explained that current NHS treatments are not effective at managing symptoms or progression, and are not licensed for treating desmoid tumours. The clinical experts also highlighted the heterogenous nature of desmoid tumours, and that treatment options will depend on where they are located. They stated that for extra-abdominal desmoid tumours, which are usually sporadic, chemotherapy would be used for symptom management unless the tumour is in a location that is imminently life threatening, in which case surgery may be considered. Intra-abdominal desmoid tumours, which are usually FAP-associated, are less likely to be associated with pain, and treatment focuses more on removing obstructions. In these cases, fewer people have chemotherapy and are more likely to have surgery. The clinical experts suggested that there is probably a lot of variation in treatment across the NHS, as different oncologists would use different chemotherapy and doses. The committee noted that treatment decisions are largely dependent on the location of the desmoid tumour and associated symptoms, with treatment options varying across the NHS. The committee acknowledged the limited treatment options for desmoid tumours and the unmet need for effective treatments.

Comparators

3.3 The comparators in the NICE scope included established clinical management, such as chemotherapy or TKIs, and best supportive care. The committee recalled that TKIs are not routinely commissioned in the NHS for the treatment of desmoid tumours (see section 3.2), so they are not a relevant comparator. The clinical experts noted that they would not routinely use the term ‘best supportive care’, which is more commonly used with cancer, and instead use ‘symptom management’. The original

company submission did not include chemotherapy as a comparator. At technical engagement, the company provided evidence comparing nirogacestat with chemotherapy (see section 3.5), but maintained that chemotherapy was not a relevant comparator. The EAG thought that chemotherapy was a relevant comparator because it is the primary systemic treatment for desmoid tumours. This was supported by EAG-sought clinical expert opinion. But most clinical and patient experts during technical engagement said that chemotherapy should not be included because it is an 'experiment over treatment', with limited evidence in desmoid tumours. The clinical experts explained that estimating the extent of off-label chemotherapy use is difficult and uncertain. They considered that off-label chemotherapy would be used in approximately 30–50% of cases, particularly for people with sporadic tumours (see section 3.2), but they noted that this is only because there are limited treatment options. The patient experts explained how chemotherapy was ineffective for them in controlling growth and did not help with their pain. The committee acknowledged that there was an unmet need in treatment options for desmoid tumours but concluded that as chemotherapy is currently used in this population, it should be included as a comparator. Therefore, the committee concluded that 'best supportive care' (symptom management) and chemotherapy were the 2 relevant comparators in this appraisal.

Clinical evidence

3.4 The pivotal trial included in the company submission was De-Fi, a phase 3, multicentre (2 in the UK), double-blind trial comparing nirogacestat with placebo in adults with progressing desmoid tumours (at least a 20% increase in the sum of diameters within 12 months, according to RECIST [response evaluation criteria in solid tumours]). The double-blind period of the study was about 20 months, before moving to an open-label phase. The primary outcome was progression-free survival (PFS), and key secondary outcomes included objective response rate (ORR) and change in patient-reported outcomes from baseline, including

pain (measure with the Brief Pain Inventory – Short Form [BPI-SF]). Overall, PFS was longer in the nirogacestat group than the placebo group. A clinical expert highlighted that in De-Fi, there was a small FAP group (n=11 for nirogacestat, n= 3 for placebo), but that inclusion in this group was based on a family history of FAP, which would not be an appropriate way to identify FAP-associated desmoid tumours. The expert said that studies investigating FAP would use genetic testing to confirm diagnosis. They noted that in De-Fi only 11 people in the overall placebo group had FAP, identified through APC genetic testing, which did not align with the 13 who had a family history. The committee noted the issues with the FAP-associated subgroup, but these did not affect the conclusions on effectiveness in the overall population. It concluded that the clinical evidence was acceptable for decision making.

Indirect treatment comparisons

3.5 There was no direct evidence comparing nirogacestat with chemotherapy. The original company submission did not include chemotherapy as a comparator and so did not include an indirect treatment comparison (ITC) with chemotherapy. The EAG did a 'pragmatic' Bayesian network meta-analysis (NMA) with fixed effects, which used a published NMA (Ou et al. [2024]) to identify 3 relevant randomised controlled trials:

- De-Fi, comparing nirogacestat with placebo
- Gounder et al. (2018), a double-blind phase 3 trial comparing sorafenib (a TKI) with placebo
- DESMOPAZ, an open-label phase 2 trial comparing pazopanib (a TKI) with methotrexate plus vinblastine (chemotherapy).

The EAG did not identify any additional studies through informal searches or clinical expert advice. The EAG noted that methotrexate plus vinblastine was not commonly used in the UK, but it was not aware of any high-quality evidence for more relevant chemotherapies. Sorafenib and pazopanib are both TKIs, and clinical expert advice to

the EAG said that these could be considered similarly effective. The outcomes of interest indirectly compared across the network were ORR, PFS and adverse events of grade 3 or higher, because the EAG stated that these were the most relevant for a cost-effectiveness analysis. The NMA results showed that nirogacestat had a statistically significant benefit over placebo across all 3 relevant outcomes and had a statistically significant benefit over chemotherapy in ORR. The benefit over chemotherapy was not observed for PFS, but the EAG noted that because of between-trial differences for PFS, a conclusion could not be made for this outcome. There were significantly fewer grade 3 or higher adverse events with nirogacestat than with chemotherapy. The EAG said that pain was also an important outcome, but a network for pain could not be established because pain outcomes were inconsistently reported across the included studies.

The EAG considered the pragmatic NMA it conducted to have serious limitations. Therefore, at technical engagement the EAG asked the company to provide a more robust approach to the NMA, informed by a systematic literature review. In its technical engagement response, the company stated that a robust NMA was not feasible, maintaining that chemotherapy was not a relevant comparator (see section 3.3), and citing the absence of a common comparator, inconsistent baseline reporting and heterogeneity in the desmoid tumour evidence base. As a result, the company did not provide an NMA and instead submitted an unanchored matching-adjusted indirect comparison (MAIC), informed by a systematic literature review that identified 4 potential studies. The company excluded 3 of these studies, explaining that 2 were abstracts of retrospective studies with small sample sizes and limited reporting. A third study (Palassini et al. [2017]) was excluded because of extensive limitations in study design, population and outcome assessment. The remaining study, DESMOPAZ, was used to inform the MAIC alongside De-Fi. The EAG considered that the justifications provided by the company for excluding the other 3 studies identified in its systematic

literature review were not sufficiently robust, and noted that limiting the evidence base in this way was likely to reduce the confidence in the resulting estimates. The company stated that there was sufficient overlap in key baseline covariates between the DESMOPAZ and DeFi trials to support 4 separate MAICs for the following outcomes: ORR (including complete response, partial response, stable disease and progressive disease) and PFS. Between-trial differences in patient and disease characteristics were adjusted for using MAIC weighting. Covariates adjusted for in the MAIC were selected based on the literature review and clinical input, and included intra-abdominal tumour location, age, and previous treatments. The company considered an MAIC to be more appropriate than an NMA, stating that differences between trials and potential treatment-effect modifiers could be more effectively adjusted for using this approach. The company also noted that any NMA would comprise a sparse network without a shared comparator. The company acknowledged that both the EAG's NMA and its MAIC had limitations. In response to the committee's question about why 4 separate MAICs were undertaken rather than a single MAIC estimating multiple outcomes, the company explained that this was a pragmatic decision made within the time constraints of the technical engagement period. It stated that, within the time available, it was simpler to implement separate MAICs for each response category than to develop a single MAIC framework or an alternative approach such as a simulated treatment comparison (STC). The company also stated that it expected this approach to produce results similar to those that would have been obtained using an STC.

The MAIC results are commercial in confidence so cannot be reported here, but the company stated that nirogacestat was either comparable to, or numerically better than, chemotherapy across all outcomes. The EAG highlighted that the company used 4 separate MAICs in the model: 1 each for complete response, partial response, stable disease and progressed disease. Separate treatment effects were estimated for

each outcome and applied to the state occupancy observed in the nirogacestat arm of the De-Fi trial to model state occupancy for people receiving chemotherapy. The EAG noted that applying 4 separate MAICs independently to each response category led to an implied expansion of the modelled population in the chemotherapy arm, with summed state occupancy equivalent to over 100% of a patient. This is not feasible, as the total modelled population should not exceed 1 patient. As a result, the company normalised the model so that state occupancy summed to 1 patient. The EAG noted that there was a lack of transparency in the company methods, particularly in how the matching variables were chosen, and it could not validate the company's approaches to do the MAIC. It also stated that 4 separate ITCs with 4 separate treatment effects was not mathematically coherent, evidenced by the need to normalise, and that relying on progressed disease (which used specific time points) instead of PFS (which used Kaplan–Meier data) added further uncertainty. On this basis, and despite its limitations, for its base case the EAG preferred to use its pragmatic NMA using ORR and assume that PFS for chemotherapy would be the same as for placebo.

Because the committee concluded that chemotherapy was a relevant comparator (see section 3.3), it considered that there needed to be an ITC between nirogacestat and chemotherapy. The committee recognised that both the pragmatic NMA and the MAIC were subject to substantial limitations, including how trial differences and treatment-effect modifiers were adjusted for. It therefore concluded that neither approach was suitable for decision making and that the associated results were highly uncertain. But the committee agreed that, in this appraisal, an NMA was its preferred approach. It therefore requested a more extensive literature review to identify additional studies that might inform a wider network. The clinical expert at the committee meeting highlighted a recently published study of liposomal doxorubicin for treating desmoid tumours (Xu et al. [2026]), which the

committee noted could be included in a network. In addition to identifying further studies, the committee requested that any NMA adjust for baseline risk, which may require informed priors. The committee also requested a full assessment of treatment-effect modifiers and prognostic factors, including clarity on which factors could and could not be adjusted for in any indirect comparisons, and the potential impact of factors that could not be accounted for. Although not its preferred approach, and subject to the feasibility of constructing a sufficiently robust NMA, the committee considered that an anchored MAIC using Xu et al. (2026) and De-Fi could be used as a secondary option.

Company model

3.6 The company submitted a semi-Markov model comparing nirogacestat with 'best supportive care' in people with progressing desmoid tumours who needed systemic treatment. The EAG updated the model to also include chemotherapy as a comparator for its base case, using evidence from the NMA (see section 3.5). The model applied 28-day cycles, with half-cycle correction to drug costs, over a lifetime horizon. The EAG noted that half-cycle correction was not appropriate because the treatment pack size was the same as the cycle length, but it did not consider this a key area of uncertainty. The model contained 5 health states: stable disease, complete response, partial response, progressed disease and death. The states were used in 2 different phases, during and after treatment, between which the structure and state interactions differed. The EAG clinical experts said that these health states reflected clinical practice. The EAG also noted that the company did not apply any resource use for complete response, and underestimated specialist visits with the other health states. Informed by clinical opinion, the EAG preferred a higher number of specialist visits for all health states, and an increased number of GP visits for stable disease. The clinical experts stated that they would still expect to see people who have a complete response to treatment or stop systemic therapy. The committee concluded that the overall structure

of the model was suitable for decision making. The committee preferred to apply higher resource use values from the EAG base case, as this better reflected clinical practice.

Utility values

3.7 Although the De-Fi trial did not collect EQ-5D data, it did collect quality-of-life data using the EORTC QLQ-30. But the company did not provide the EORTC QLQ-30 data in its submission or during technical engagement. The company said that this was because the EORTC data could not be robustly mapped to the EQ-5D and that the results lacked face validity, making them unsuitable for decision making. The utility values in the company base case were instead informed by published utility values from people with soft-tissue sarcoma (Shingler [2013]). The company considered that soft tissue sarcoma was a reasonable surrogate for desmoid tumours because of similarities in origin, clinical presentation, symptoms, diagnostic and treatment pathways, and management by oncologists or sarcoma specialists. The EAG stated that the utility value for progressed disease was implausibly low for people with desmoid tumours (0.263). It explained that Shingler (2013) was a time-trade-off study, which does not align with the NICE reference case. The EAG believed that using mapped data from De-Fi would be most appropriate, but given that this data was not provided, the EAG preferred using utility values based on EQ-5D data from a clinical trial of people with soft-tissue sarcoma (Reichardt [2012]). This resulted in a utility value of 0.560 for progressed disease. The clinical expert explained that using soft tissue sarcoma may be reasonable given the widespread anatomical distribution of both diseases but noted that it was not optimal. The company explained that the EORTC in De-Fi was a secondary outcome, measuring change in baseline up to cycle 10, and the trial was not designed to be sufficiently powered to measure quality of life throughout the full course of treatment, especially through progression. The company highlighted various data limitations. It said that there was a temporal mismatch between the EORTC data and RECIST as they were assessed at different timepoints.

It noted that people in the trial were not monitored after disease progression, so there was a lack of data. In addition, the mapping algorithm was based on a patient population with cancer, which would introduce additional uncertainty. The company said that, although the utilities from Shingler (2013) were not from a desmoid tumour population, they provided more plausible estimates, and this was supported by clinical and patient feedback. But the company acknowledged that uncertainty remained. The committee acknowledged the challenges in mapping the utilities from De-Fi, but was concerned that trial quality-of-life data and the mapping results were not presented for validation. The committee noted that for some people with progressed desmoid tumours, quality of life may be substantially impacted. The committee was aware that the utility values represented the quality of life for the average person with desmoid tumours in each health state. The committee agreed that the utility values could represent some people with progressed desmoid tumours but that for the average person, the utility value for progressed disease of 0.263 was likely to be too low. The company acknowledged that the true utility value of progressed disease was likely between those in the company (0.263) and the EAG (0.560) base cases. The committee also noted that while soft-tissue carcinoma has a similar disease distribution to desmoid tumours, it is unclear whether the diseases are similar enough to justify using soft-tissue carcinoma as a proxy for utilities. The committee therefore concluded that it would need to see the EORTC QLQ-30 quality-of-life data from De-Fi alongside the results of mapped to EQ-5D, as well as further justification about how soft-tissue carcinoma and desmoid tumours are similar.

Pain as an outcome

3.8 Patient-reported pain was a key secondary outcome in De-Fi, which reported a statistically significant difference in BPI-SF score for nirogacestat compared with placebo. But the EAG noted that the efficacy of reducing pain was unclear because this difference did not translate into a clinically meaningful benefit (the results are commercial in confidence

and cannot be reported here). The EAG further explained that it was unclear whether this reflected a lack of clinically meaningful benefit, or whether it was because De-Fi included participants who did not have uncontrolled pain at baseline. The EAG was unable to include pain as an outcome in the NMA because a network could not be established. As described in section 3.2, the EAG's clinical experts noted pain reduction as a key treatment benefit for chemotherapy, and that there can be pain reduction without tumour shrinking. But patient experts at technical engagement and the committee meeting stated that chemotherapy does not have a positive impact on pain and gives very little symptomatic relief. The clinical experts added that pain is a major issue with sporadic desmoid tumours, especially extra-abdominal tumours, but was less of an issue in FAP-associated desmoid tumours.

At technical engagement, the company clarified that 39% people in the nirogacestat group and 43% in the placebo group in De-Fi had uncontrolled pain at baseline. The company provided a post-hoc analysis for subgroups with controlled and uncontrolled pain at baseline, and reported that both groups showed a clinically meaningfully improved pain at cycle 10 (each cycle in De-Fi was 28 days). But the improvement was greater in the group that had uncontrolled pain at baseline (the results are commercial in confidence so cannot be reported here). The EAG highlighted that the result for the uncontrolled-pain-at-baseline group at cycle 10 was actually slightly below the minimally important difference value but met the minimally important difference threshold in cycles 9 and 11. Therefore, the EAG interpreted these results as a clinically meaningful reduction in pain. The EAG also highlighted that company data showed that response rate and pain were reasonably well correlated in the nirogacestat group. The committee agreed that improving pain is an important outcome for most people with desmoid tumours and should be included in the economic model if possible. It also noted that pain is included in quality-of-life questionnaires, such as the EORTC questionnaire used in the De-Fi study. The committee recalled its request

to see the De-Fi quality-of-life data (see section 3.7), which was not provided by the company. The committee considered that quality-of-life data from De-Fi may adequately capture pain in the model.

Stopping rule

3.9 In its base case, the company assumed that all people having nirogacestat would stop treatment after 2 years. The EAG noted that experts broadly supported stopping treatment after 2 years, but only if there was flexibility to continue for longer if the tumour was still shrinking, or restart treatment if needed, for example, if the tumour started growing again. So, the EAG base case applied a 2-year stopping rule informed by clinical experts, with criteria that allowed 15% of patients to continue treatment beyond 2 years, with 100% of people off treatment by 3 years. The EAG noted that the model did not allow for restarting treatment. The company provided data on tumour size plateaus and said that by Year 2, 100% of tumours had plateaued in people with complete and partial response and more than 75% of tumours in people with stable disease. The company stated that a 3-year stopping rule would overestimate the number of people who continue treatment after 2 years. The committee noted that there were now 4-year follow-up data for De-Fi, and so trial data on treatment duration should be available to inform how long people stay on treatment in the model. The committee also discussed the issue of stopping and restarting treatment. It recalled that retreatment with nirogacestat was not permitted in DeFi, so the trial did not provide evidence on restarting treatment after discontinuation. The clinical and patient experts emphasised that in clinical practice the ability to restart treatment would be important. They noted that only a small proportion of people would be expected either to continue treatment beyond 2 years or to restart treatment later. The NHS England expert noted that the summary of product characteristics for nirogacestat says that treatment can be continued until disease progression or toxicity, and does not include a stopping rule. The committee acknowledged that, although a strict 2-year stopping rule would be straightforward, it is important for

people with desmoid tumours to be able to restart or extend treatment if needed, so a 2-year stopping rule is not universally appropriate for everyone. It also recalled that there is no stopping rule in the summary of product characteristics for nirogacestat. The committee noted that any criteria for stopping at 2 years, continuing beyond 2 years and restarting treatment would need to be clear, clinically appropriate and implementable in the NHS. So, the committee concluded that the model should apply robust and clinically driven criteria to inform a 2-year stopping rule with allowances for continuing treatment beyond 2 years and restarting treatment. This could be informed by clinical expert input or data on the proportions of people who continue treatment beyond 2 years and the proportion who need re-treatment, if available. The committee would like to see scenarios exploring the impact of different criteria, such as varying the proportion of people who need re-treatment and a scenario with no stopping rule.

Treatment discontinuation

3.10 The company assumed that everyone in the nirogacestat arm would continue treatment, unless they have disease progression, for 2 years. The EAG said that this assumption did not reflect what was seen in De-Fi, in which some patients stopped treatment because of treatment-related adverse events before 2 years (the data is commercial in confidence and cannot be reported here). The EAG preferred to model discontinuation to reflect De-Fi. At the meeting, the company agreed that using the discontinuation data from the trial would be appropriate. The committee also agreed, but noted that treatment discontinuation should be applied appropriately alongside any criteria for stopping and restarting nirogacestat (see section 3.9).

Ovarian dysfunction

3.11 The committee noted that the De-Fi trial reported that a high proportion of people with childbearing potential in the nirogacestat group (75%) experienced ovarian dysfunction, an umbrella term covering amenorrhea,

premature menopause, menopause and ovarian failure. Ovarian dysfunction was resolved in 79% of cases during the treatment period. The committee noted concerns that this meant that ovarian dysfunction did not resolve in 21% of cases. The company explained that no grade 3 or higher adverse events related to ovarian dysfunction occurred during the trial period. Ovarian dysfunction was included in the economic model as a one-off event that occurred at the start of the model for a specific duration (the exact duration is confidential and cannot be reported here). The EAG's clinical experts explained that ovarian dysfunction is also a risk with chemotherapy; this is explained to people of childbearing potential, and they are offered ovarian preservation. The EAG's clinical experts expected that the same process would be in place for nirogacestat. The committee noted that ovarian dysfunction covers a wide range of conditions that can have a significant impact on the person, healthcare requirements and costs, which may not be captured in the model. The committee recalled how patient experts described the impact of desmoid tumours on family life, including concerns about the ability to plan for, or have, the option of starting a family. The EAG stated that it was possible to model the impact of ovarian function on utilities, but the impact on fertility was more challenging. The committee was concerned that the impact of treatment-related effects on fertility and reproductive health had not been fully explored in the model, particularly in relation to costs and quality-adjusted life years. It therefore requested additional data from the company to understand the impact of nirogacestat on the specific conditions encompassed by ovarian dysfunction.

Cost-effectiveness estimates

Acceptable ICER

3.12 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 per quality-adjusted life year (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 presented ITCs were not suitable for decision making (see section 3.5)
- it is unclear whether using soft-tissue sarcoma utilities as a proxy for utilities is justified, and the De-Fi trial utility values had not been presented for validation or used in the economic model (see section 3.7)
- a hard stopping rule was inappropriate and there needed to be clear, informed criteria for a flexible stopping rule that includes restarting treatment (see section 3.9).

Because of these uncertainties, the committee could not determine a plausible ICER or maximum acceptable ICER.

Committee preferences

3.13 Both the company's and the EAG's base-case ICERs were above the range that NICE considers an acceptable use of NHS resources. The exact cost-effectiveness estimates cannot be reported here because of confidential discounts. The committee's preferred assumptions were that:

- chemotherapy should be included as a comparator (see section 3.3)
- treatment discontinuations should be aligned to the De-Fi trial (see section 3.10)
- resource use, in the form of healthcare visits, should reflect the EAG base case (see section 3.6).

Committee requests for additional analyses

3.14 The committee requested the following additional analyses:

- The ITC should be a fully informed NMA with a wider network and adjustment for baseline risk or an anchored MAIC (see section 3.5).

- Utility values from De-Fi should be presented and mapped to EQ-5D (see section 3.7).
- Pain should be captured, and may be accounted for if the De-Fi trial utilities are used (see section 3.8).
- A flexible 2-year stopping rule that is implementable in the NHS and allows some people, according to specific criteria, to continue or restart nirogacestat after 2 years, informed by clinical expert input. In addition to this, analyses with no stopping rule (see section 3.9).
- Data showing the impact of nirogacestat on ovarian dysfunction (see section 3.10).

Other factors

Equality

3.15 The committee noted the evidence that the incidence of desmoid tumours is higher in women and during pregnancy. It also recognised that desmoid tumour biology is influenced by oestrogen exposure, which may be relevant to people with current or prior oestrogen exposure, regardless of gender identity. In addition, the committee noted that desmoid tumours are more commonly diagnosed in younger people, particularly those of reproductive age. Sex, pregnancy and maternity, and age are protected characteristics under the Equality Act 2010. But, because its recommendation does not restrict access to treatment for some people over others, the committee agreed that these were not potential equalities issues.

Uncaptured benefits

3.16 The committee considered whether there were any uncaptured benefits of nirogacestat. It noted that desmoid tumours can also have a severe impact on carers' quality of life. The clinical expert also explained that people with desmoid tumours, particularly intra-abdominal tumours, may need stomas, ureteric stents and home intravenous nutrition. The need for these may be reduced if nirogacestat was available. They also explained

that people with FAP have a higher risk of cancer, including duodenal and gastric cancer, but curative or risk-reducing surgery can be impossible with desmoid tumours present. They explained that nirogacestat may reduce the desmoid tumour burden, allowing some people to have cancer-removing surgery who otherwise would not be able to. The committee concluded that these considerations would be reflected when determining an acceptable ICER.

Conclusion

Recommendation

3.17 The committee recalled that both the company's and EAG's base-case ICERs were above the range that NICE considers an acceptable use of NHS resources. Because of the uncertainties with the ITC and some of the modelling assumptions, the committee was not able to determine the most plausible ICER and requested additional analyses (see section 3.14). So, nirogacestat should not be used.

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 B. 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

Baljit Singh

Vice chair, technology appraisal committee B

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.

Lauren Elston

Technical lead

Nigel Gumbleton

Technical adviser

Jeremy Powell

Project manager

Jeremy Dietz

Principal technical adviser

ISBN: [to be added at publication]