NICE National Institute for Health and Care Excellence

NICE guidance

Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Regorafenib is recommended as an option for treating unresectable or metastatic gastrointestinal stromal tumours in adults whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib, only if:

- their Eastern Cooperative Oncology Group (ECOG) performance status is 0 to 1 and
- the company provides regorafenib with the discount agreed in the patient access scheme.

1.2 When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

1.3 These recommendations are not intended to affect treatment with regorafenib that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for unresectable or metastatic gastrointestinal stromal tumours after disease progression on, or intolerance to, prior treatment with imatinib and sunitinib is best supportive care.

The evidence shows that people having regorafenib have longer before their disease progresses compared with those having best supportive care. However there is some uncertainty around how long regorafenib increases the overall length of time people live compared with those on best supportive care.

Regorafenib meets NICE's criteria to be considered a life-extending end-of-life treatment, and the most plausible cost-effectiveness estimate is around £44,000 per quality-adjusted

life year gained. Therefore it can be recommended for use in the NHS.

Regorafenib is only recommended for people who have an ECOG performance status of 0 to 1 because in clinical practice, regorafenib is only expected to be used in people who have an ECOG performance status of 0 to 1; there is limited evidence for its use in people with a performance status of 2 or more.

2 Information about regorafenib

Marketing authorisation

2.1 Regorafenib (Stivarga, Bayer) is indicated 'for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib'.

Recommended dose and schedule

2.2 The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.

Price

2.3 £3,744.00 for 84 tablets of 40 mg (excluding VAT; British national formulary [BNF] edition 72).

2.4 The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of regorafenib, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee considered evidence submitted by Bayer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

Best supportive care is the most appropriate comparator

3.1 The patient and clinical experts explained that gastrointestinal stromal tumours (GIST) are a rare disease that often takes years to diagnose because people have non-specific symptoms. The clinical expert advised that first-line treatment for metastatic GIST is imatinib, which is generally well tolerated. Once disease has progressed, patients are switched to sunitinib, which on average gives 6 to 12 months benefit before the disease progresses again but has more side effects than imatinib and requires careful monitoring. The patient and clinical experts explained that there are no alternative third-line treatment options after disease progression or if patients are intolerant to imatinib and sunitinib other than best supportive care. Regorafenib is currently available on the Cancer Drugs Fund for metastatic GIST after disease progression or intolerance to imatinib and disease progression after sunitinib, only if the patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. The clinical expert explained that the only alternative to best supportive care and regorafenib (through the Cancer Drugs Fund) was to participate in a clinical trial but noted that these were rare. The committee concluded that best supportive care is the most appropriate comparator for this appraisal.

Treatment options

People with unresectable or metastatic GIST would greatly value another treatment option

3.2 The patient experts advised that regorafenib is well tolerated, with side effects (such as sore feet and hands, constipation and diarrhoea) that can be managed. The clinical experts described how dose adjustments and scheduling were important in treating GIST and that these are managed on an individual basis to achieve a balance between the minimal effective dose and side effects that can be tolerated. The patient experts explained that regorafenib allows people to remain actively engaged in work and family life, while reducing anxiety and increasing quality of life. Regorafenib also provides an important further treatment option to people who cannot tolerate sunitinib. One patient expert described how extending life was a priority to enable patients to spend more time with their families and it was important to be able to lead a near-normal life while having treatment. The committee recognised the importance of a potentially life-extending treatment with manageable side effects. The committee concluded that a treatment option for people with metastatic or unresectable GIST after imatinib and sunitinib would be greatly valued, particularly if it extended life and had manageable side effects.

Clinical evidence

Treatment with regorafenib in the GRID trial is in line with clinical practice

3.3 The evidence for regorafenib submitted by the company came from GRID, a multicentre double-blind randomised controlled trial with 199 patients who had previously had treatment with imatinib and sunitinib. It compared regorafenib plus best supportive care (133 patients) with placebo plus best supportive care (66 patients). Best supportive care included various treatments such as analgesics, radiation therapy for pain control and palliative surgery. After disease progression, patients receiving placebo were given the option to cross over to

regorafenib, and patients already receiving regorafenib were offered open-label regorafenib if it was considered clinically beneficial. In the trial, treatment could be delayed or reduced according to a pre-specified schedule. The clinical experts confirmed that dose reductions were common in clinical practice, because of the side effects associated with regorafenib, and managed on an individual basis. The clinical experts explained that treatment would only be stopped in clinical practice if there was clear disease progression and worsening clinical symptoms. Clinical guidelines recommend continued treatment with tyrosine kinase inhibitors as long as there is continued benefit. The clinical experts also advised that there was uncertainty around whether patients in the GRID trial could have other off-label treatments after disease progression that are not standard practice in the NHS. The committee concluded that using regorafenib after disease progression was in line with the marketing authorisation and current clinical practice.

Performance status should be taken into account in the final recommendations

3.4 Patients in the GRID trial had an ECOG performance status of 0 to 1 and the summary of product characteristics for regorafenib states that there are limited data in patients with a performance status of 2 or above. Regorafenib is currently provided by the Cancer Drugs Fund to people who have a performance status of 0 to 1, in line with trial evidence. The clinical experts explained that very few people for whom regorafenib would be considered present with a performance status of 2 in clinical practice; this is because treatment is actively managed in specialist centres to prevent performance status from deteriorating, particularly given the tolerability issues associated with sunitinib. The committee concluded that in line with the clinical evidence and the use of regorafenib in clinical practice, it would take performance status into account when making its final recommendations.

Correcting for crossover in the GRID trial is appropriate for estimating overall survival

3.5 In the GRID trial there was a high level of crossover (88%) from the placebo arm to open-label regorafenib after disease progression. The company and the ERG

agreed that a statistical correction for crossover was needed to produce unbiased estimates of overall survival in the placebo arm. The company carried out 2 crossover corrections using the iterative parameter estimation (IPE) and rank preserving structural failure time (RPSFT) methods. Both methods aimed to reconstruct individual patient data for overall survival in the placebo arm as if there had been no crossover. The ERG advised that both the IPE and RPSFT methods were appropriate for correcting crossover. The committee concluded that given the high level of crossover from placebo to regorafenib, an intention-to-treat analysis was not appropriate and a statistical correction for overall survival was needed.

Survival results from the GRID trial

Regorafenib is clinically effective in improving progression-free survival compared with best supportive care

3.6 Data from 2015 from the GRID trial showed that regorafenib improved progression-free survival (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.19 to 0.39). Data from 2017 showed that after crossover correction, median overall survival in the placebo arm was around 8 months compared with 17.4 months for regorafenib. The 2017 data showed a larger overall survival benefit after correcting for crossover (unadjusted HR 0.90; 95% CI 0.68 to 1.19, RPSFT HR 0.48; 95% CI 0.07 to 3.33, IPE HR 0.45; 95% CI 0.06 to 3.69). The committee understood that although not statistically significant, the point estimates did show improved overall survival with regorafenib. The committee concluded that there was evidence that regorafenib is clinically effective in improving progression-free survival compared with best supportive care but that there was uncertainty about the magnitude of overall survival benefit.

The company's economic model

The company's survival model is appropriate for decision-making

3.7 The company submitted a partitioned survival model with 3 health states (progression free, progressed and death) that used survival data from the GRID trial. The company's base case modelled treatment duration by using the treatment discontinuation curve from GRID. Therefore the company's base case included the additional cost of regorafenib in the treatment arm after disease progression in line with the GRID trial (open-label regorafenib was offered to patients randomised to regorafenib after progression if it was considered clinically beneficial). Use of regorafenib after disease progression is in line with clinical practice (see section 3.3). The company's base case also incorporated dose intensity by including the mean observed dose of regorafenib from GRID (including doses of 0 mg). The ERG agreed that the company's approach to modelling treatment duration and dose intensity was appropriate. The committee concluded that the company's model, using trial data to model treatment duration and dose intensity and including the additional cost of regorafenib after disease progression, was appropriate for decision-making.

Overall survival data from the GRID trial

There is uncertainty in the adjustment for overall survival but analyses using 2017 data are acceptable

3.8 The company's base case included overall survival estimates based on the most recent data from GRID (2017 data). The ERG initially had several concerns with using the 2017 data related to:

- methodological assumptions in the treatment switching adjustment
- the impact of recensoring on adjusted overall survival and the cost effectiveness of regorafenib
- reasons for a large decrease in overall survival in the placebo arm after

adjusting for treatment switching when using the 2017 data compared with the 2015 data.

Using different data cut-offs for estimating overall survival had a large impact on the cost-effectiveness results. Regorafenib appeared to be more cost effective when using the 2017 data for overall survival than when the 2015 data were used. The company responded to the ERG's concerns with additional explanations, and the ERG accepted the company's rationale and justifications of the methods used. The ERG confirmed that there was no conclusive evidence that the company had performed the treatment switching adjustment incorrectly, and accepted it was appropriate to use the most recent (2017) data. The committee concluded that while there was some remaining uncertainty, the analysis using 2017 data for estimating overall survival was acceptable.

Crossover correction

Both RPSFT and IPE adjustments of overall survival should be considered

3.9 The company's base case included an estimated treatment effect for overall survival with an IPE crossover correction. The ERG advised that the IPE method is an extension to the RPSFT method using parametric methods and the assumption of a common treatment effect (that is, people receive the same treatment benefit regardless of when they receive treatment). This assumption may not hold if people in the trial were able to receive a variety of off-label treatments after disease progression (see section 3.3). The ERG noted that both the IPE and RPSFT methods were appropriate and gave similar estimates of overall survival for the placebo arm (median overall survival IPE 8.0 months and RPSFT 8.4 months). In its revised explorations, the ERG considered both IPE- and RPSFT-corrected overall survival estimates as acceptable. The committee recognised that using the RPSFT rather than the IPE method did not have a large impact on the cost-effectiveness estimate of regorafenib. The committee concluded that cost-effectiveness results using either IPE or RPSFT adjustments should be considered in its decision-making.

Recensoring to avoid bias

Analyses with and without recensoring should be considered

3.10 The company's base case included an IPE adjustment with recensoring (in line with guidance from the Decision Support Unit). Recensoring is used to reduce the risk of bias associated with a treatment-switching adjustment, and recensoring data at an earlier time point aims to avoid informative censoring (because treatment switching is not random). The ERG advised that recensoring may lead to biased estimates of the average treatment effect when the proportional treatment effect assumptions do not hold, and there is some academic debate on whether to use recensoring because the estimated treatment effect is generally larger when it is used. The company provided further analyses that explored the impact of recensoring. The ERG advised that it was appropriate to consider analyses with and without recensoring. The committee noted that recensoring had a large impact on the cost-effectiveness estimate and that regorafenib appeared to be more cost effective if recensoring was used. The committee concluded that the arguments for and against recensoring were evenly balanced and that results both with and without recensoring should be considered when assessing the cost effectiveness of regorafenib.

Extrapolation of overall survival

A shorter-tailed Weibull distribution is appropriate for estimating overall survival and is clinically plausible

3.11 The company's base case included a log-logistic extrapolation of overall survival because it provided the best fit to the trial data from GRID. The company highlighted that log-logistic, Weibull and Gompertz models were considered clinically plausible by the clinical experts. The ERG advised that clinical plausibility of extrapolations was critical and the evidence for longer-tailed and shorter-tailed distributions appeared to be evenly balanced. The clinical experts explained that very few people with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, treatment with imatinib and

sunitinib will survive for 10 years. The choice of extrapolation method for estimating overall survival had a large impact on the cost-effectiveness results for regorafenib. A log-logistic extrapolation resulted in a larger proportion of people surviving after 10 years compared with the Weibull extrapolation and the clinical experts and committee considered this to be optimistic. The committee agreed that a Weibull extrapolation would be more appropriate because it had a shorter tail length and more plausibly reflected the survival of people at this stage of the disease. It noted that in the company's base case, regorafenib became less cost effective when the Weibull and Gompertz models were used. The committee concluded that an overall survival extrapolation that used a shorter-tailed Weibull model was most appropriate because it best reflected the survival outcomes of the population.

Including additional background mortality is appropriate

3.12 The ERG explained that causes of mortality in the GRID trial would largely be related to GIST but it was likely that additional general mortality would have occurred after the trial ended. The ERG's base case incorporated this additional background mortality but the company's did not. The committee understood that the impact of background mortality was likely to be lower when a shorter-tailed Weibull extrapolation was used. The committee concluded that including an adjustment for general mortality was appropriate.

Utility values

Including age-related utility decrements is appropriate

3.13 Utility estimates for health-related quality of life were taken from the GRID trial, which reported the EQ-5D and European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). Both the company and ERG base cases used EQ-5D data from paired samples that were not split by treatment arm. The company stated that a repeated measures analysis would have been biased because more measurements were taken when patients did not have disease progression and there were no clinically meaningful

differences in EQ-5D between the treatment arms. The ERG's base case also applied age-related utility decrements because utility often declines with age; this was not included in the company's base case. The committee understood that the addition of age-related utility decrements did not have a large impact on the cost-effectiveness results. The committee concluded that including age-related utility decrements was appropriate.

End of life

Regorafenib meets the end-of-life criteria

3.14 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. In the GRID trial the adjusted median overall survival in the placebo plus best supportive care arm was less than 12 months (RPSFT-corrected median overall survival 8.4 months and IPE-corrected median overall survival 8.0 months). The company's economic model predicted mean undiscounted life years of 0.97 for the IPE-adjusted placebo arm and 1.01 for the RPSFT-adjusted placebo arm when recensoring was applied. The committee concluded that regorafenib was indicated for people with a short life expectancy. The median overall survival improvement in the GRID trial was at least 9 months for patients treated with regorafenib compared with those having best supportive care, depending on which crossover correction method was used. The crossover-corrected mean overall survival benefit for regorafenib was around 1.2 years longer compared with best supportive care in the ERG's revised base case, but less than 1.2 years when recensoring was used (estimates taken from the company's economic model). The committee concluded that regorafenib offered an extension to life of at least 3 months compared with best supportive care.

Cost-effectiveness results

Regorafenib is a cost-effective use of NHS resources

3.15 The committee considered the cost effectiveness of regorafenib as estimated using its preferred analyses, which included:

- 2017 data for overall survival (see section 3.8)
- crossover adjustment using either RPSFT or IPE (see section 3.9)
- analyses with and without recensoring (see section 3.10)
- overall survival extrapolation using a Weibull distribution (see section 3.11)
- background mortality (see section 3.12)
- age-related utility decrements (see section 3.13).

The committee discussed that, using its preferred analyses, the incremental cost-effectiveness ratio (ICER) was likely to lie between £40,000 and £48,000 per quality-adjusted life year (QALY) gained. It concluded that the most plausible ICER was the midpoint of that range: around £44,000 per QALY gained. The committee concluded that, given that regorafenib met the criteria for being a life-extending, end-of-life treatment, it could be recommended as a cost-effective use of NHS resources.

Other factors

The committee did not identify any other factors that affected its recommendations

3.16 The committee considered whether its recommendations were associated with any potential issues related to equality. The committee concluded that healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance

status and make any adjustments they consider appropriate.

3.17 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of technology.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has an unresectable or metastatic gastrointestinal stromal tumour and the healthcare professional responsible for their care thinks that regorafenib is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The Department of Health and Bayer have agreed that regorafenib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to access.team@bayer.com.

5 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

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

Abitha Senthinathan
Technical Lead

Christian Griffiths
Technical Adviser

Kate Moore
Project Manager

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