Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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regorafenib 40mg film-coated tablet (Stivarga®) SMC No. (1031/15)

Bayer plc

6 March 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission and assessed under the ultra-orphan and end of life process

regorafenib (Stivarga®) is accepted for use within NHS Scotland.

Indication under review: Treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

In a study of patients with metastatic or unresectable GIST who had prior treatment with imatinib and sunitinib, treatment with regorafenib prolonged the median progression free survival by 3.9 months when compared with placebo.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of regorafenib and is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 April 2015

Indication

Treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.

Dosing Information

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

Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs. Dose interruptions and/or dose reductions may be required based on individual safety and tolerability. Dose modifications are to be applied in 40mg (one tablet) steps. The lowest recommended daily dose is 80mg. The maximum daily dose is 160mg.

Regorafenib should be prescribed by physicians experienced in the administration of anticancer therapy.

Product availability date

July 2014. Regorafenib meets SMC ultra-orphan and end of life criteria in this treatment setting.

Summary of evidence on comparative efficacy

Regorafenib is an oral agent which inhibits various kinases involved in tumour angiogenesis, oncogenesis, and the tumour microenvironment, most notably KIT, a key enzyme associated with the oncogenesis of gastro-intestinal stromal tumours (GISTs).[3] Clinically relevant GISTs are rare tumours, with an annual incidence of approximately one in 100,000.[1] Most GISTs develop in the stomach or small intestine, and the main sites of metastasis are the liver and peritoneal cavity.[2]

The pivotal study, GRID, is an ongoing multi-centre, randomised, double-blind, placebo-controlled phase III study which recruited patients between January and August 2011.[4] Adults with histologically-confirmed, metastatic or unresectable GIST who had objective disease progression on or who were intolerant to imatinib, as well as disease progression on sunitinib were included. Patients had good performance status, Eastern Co-operative Oncology Group (ECOG) 0 or 1, and adequate hepatic, renal and bone marrow function. Patients were required to have at least one measurable lesion according to Response and Evaluation Criteria in Solid Tumours (RECIST) (version 1.1), modified to be specific to GIST.

Patients were randomly allocated in a 2:1 ratio to regorafenib 160mg daily (n=133) or placebo (n=66), for the first three weeks of a four-week cycle. Randomisation was stratified for geographical location (Asia versus rest of the world) and line of therapy (third line versus fourth line or beyond). Masked treatment was continued until occurrence of unacceptable toxicity, withdrawal from the study or disease progression. Treatment assignment was unblinded upon centrally-assessed disease progression, at which point all patients were offered open-label regorafenib. Dose adjustment or delay was permitted throughout the study based on pre-specified protocols to reduce adverse events (e.g. hypertension, hand-foot skin reaction, increases in liver function tests). All patients received best supportive care, defined as any strategy used to preserve the comfort and dignity of the patient but excluding antineoplastic therapy, such as chemotherapy, tyrosine-kinase therapy, radiotherapy or surgical intervention.[4]

Efficacy analyses were conducted in the intention to treat population and the primary outcome was progression free survival (PFS), defined as the time from randomisation to the date of first observed radiological progression (as per modified RECIST) assessed by blinded central radiologists, or death from any cause.[4,5] The primary data cut-off in January 2012 was chosen upon accrual of the planned 144 progression events: 61% (81/133) of regorafenib patients and 95% (63/66) of placebo patients. Median treatment duration was 22.9 weeks in the regorafenib group and 7.0 weeks in the placebo group. Regorafenib was associated with a significantly longer median PFS compared with placebo (4.8 months versus 0.9 months): hazard ratio (HR) 0.27 (95% confidence interval [CI]: 0.19 to 0.39), p<0.0001. There was a consistent treatment effect for PFS in favour of regorafenib across the range of sub-groups analysed.[4]

A planned interim analysis of overall survival was conducted at this point; however, 85% of placebo patients had crossed-over to regorafenib. The data were immature with 46 events accrued and median overall survival not reached in either group. There was no significant difference between the groups for overall survival (HR=0.77 [95% CI: 0.42 to 1.41], p=0.199).[4] Correction for cross-over was conducted using two methods: the rank preserving structural failure time (RPSFT), HR=0.54 (95% CI: 0.29 to 1.01, p=0.0247) and an iterative parameter estimation (IPE), HR=0.56 (95% CI: 0.30 to 1.06, p=0.0349).[5] A later ad hoc analysis on a more mature dataset was conducted in January 2014 and was based on 139 events: 91 (68%) of regorafenib patients and 48 (73%) of placebo patients. There was no significant difference between the study groups: median overall survival was 17.4 months in both and HR was 0.85 (95% CI: 0.60 to 1.21), p=0.180. This analysis was not corrected for cross-over.[5]

Other secondary outcomes included time to progression (TTP), overall response rate (ORR; the proportion of patients with complete or partial response) and disease control rate (DCR; the proportion of patients with complete or partial response or stable disease). TTP, based on central assessment, was significantly delayed in the regorafenib group compared with placebo: median TTP was 165 days versus 28 days, HR 0.25 (95% CI: 0.17 to 0.36), p<0.000001. ORRs were low: 4.5% for regorafenib and 1.5% for placebo, p=0.14. This consisted entirely of partial responses. DCR was significantly greater for regorafenib (53%) compared with placebo (9.1%), p<0.0001.[4,5]

Exploratory endpoints evaluated health-related quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EuroQol (EQ-5D) tools. Completion rates dropped over time: 92% at baseline, falling to 64% at cycle three. Global health status and the five functional dimensions measured with EORTC QLQ-C30 deteriorated slightly over time and with a similar magnitude in both groups. However, there was a clinically significant deterioration in the role function subscale in the regorafenib group. A similar deterioration in health status was measured for both treatment groups using EQ-5D, but this was only clinically significant for the change from baseline at the end of blinded treatment visit.[5]

Summary of evidence on comparative safety

In GRID, treatment-related adverse events were reported in 98% (130/132) regorafenib patients and in 68% (45/66) placebo patients. Serious adverse events were reported in 29% and 21% of regorafenib and placebo patients respectively. Adverse events were generally manageable with dose modification, rather than requiring treatment discontinuation. Dose modification was required in 72% of regorafenib patients compared with 26% of placebo patients, whereas permanent discontinuation occurred in 6.1% and 7.6% of patients respectively.[4,5]

The most common adverse events reported in the regorafenib group were: hand-foot skin reaction, hypertension, diarrhoea, fatigue and oral mucositis. Grade 3 adverse events reported in at least 5% of patients included: hand-foot skin reaction (20% versus 0% in the regorafenib and placebo groups respectively), hypertension (23% versus 3.0%), and diarrhoea (5.3% versus 0%). Only a small proportion of patients had a grade 4 adverse event: 2/132 regorafenib patients and 1/66 placebo patients.

Up to the primary efficacy data cut-off there were 10 grade 5 adverse events: seven in the regorafenib group and three in the placebo group. Three events were considered by the investigator to be treatment-related: one cardiac arrest and one hepatic failure in the regorafenib group, and fatigue in the placebo group.[4]

The European Medicines Agency (EMA) noted that the incidence of hand-foot skin reactions and hypertension was greater in patients with GIST than compared with those treated with regorafenib for metastatic colorectal cancer.[5]

Summary of clinical effectiveness issues

Regorafenib is the first treatment to be specifically licensed for use as a third-line agent in patients with unresectable or metastatic GIST following the failure of imatinib and sunitinib. Clinical guidance published prior to the availability of regorafenib recommends that patients who have failed second-line sunitinib should be considered for enrolment in suitable clinical studies, or in the absence of a trial be considered for re-challenge with imatinib.[2] The recently updated European Society of Medical Oncology guidelines recommend that regorafenib, when available, should be the standard third-line option for patients who have failed on imatinib and sunitinib.[1] Regorafenib meets SMC ultra-orphan and end of life criteria for this indication.

Treatment with regorafenib was associated with a significantly longer median PFS when compared with placebo: 4.8 months versus 0.9 months. This was supported with significant benefits demonstrated in secondary outcomes such as delayed TTP and a greater DCR.

There was no significant overall survival advantage demonstrated in the GRID study but this has been confounded by substantial patient cross-over upon disease progression. The EMA commented that median overall survival was generally longer in the GRID study when naively compared with other studies of third-line treatment post failure of imatinib and sunitinib.

There was no noteworthy difference between regorafenib and placebo in relation to changes in health-related quality of life, but this evidence is limited by low completion rates of the quality of life questionnaires.[5] Patients with an ECOG performance status of >2 were excluded from the study ;therefore, there are limited efficacy and safety data available for these patients.[3]

The marketing authorisation for regorafenib includes patients who have not tolerated sunitinib but these patients were excluded from the GRID study. The pivotal phase III study of sunitinib post imatinib reported a low discontinuation rate due to adverse events,[6] so this may not be an important limitation with the GRID study.

The company conducted an indirect comparison of regorafenib and imatinib re-challenge in patients who had prior treatment with imatinib and sunitinib. Two analyses were conducted, a Bayesian network meta-analysis and an adjusted Bucher indirect comparison. The evidence network consisted of two studies, and outcomes compared were progression free survival and overall survival. However, as a crude indicator of potential comparability of the two studies' populations, median PFS in the

common comparator groups (placebo) were the same. While the estimated HR for PFS and overall survival favoured regorafenib, without ranking of the treatments or probabilities of superiority, it is not possible to judge if there are survival benefits with regorafenib compared with imatinib.

Although adverse events were common, most can be managed with dose modification and/or interruption. This may require patients to attend clinics frequently to manage adverse events.

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of regorafenib, as an ultra-orphan and end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Patients with advanced GIST who experience progression on, or are intolerant to, imatinib and sunitinib have no other licensed treatment option at this stage in their disease and generally have very limited life expectancy of less than 12 months.

- Regorafenib offers patients around 4 months additional disease stabilisation. It may lead to a decrease in tumour volume for extended periods which in turn decreases symptoms such as pain, tiredness and shortness of breath. Overall survival of 17 months in GRID should be viewed as a considerable extension (two-fold) of good quality life. This high quality time is incredibly meaningful to patients.

- Toxicity associated with regorafenib is considered to be relatively minor. Anecdotal evidence in patients unable to tolerate the full dose suggests that dose modification is possible whilst maintaining clinical benefit.

- The PACE group felt strongly that regorafenib should be made available in NHS Scotland and that this should be in line with the licensed indication. Clinicians stressed that this would be a valuable medicine, used in a small number of patients (around 7-8 per annum) with adequate performance status and end organ reserve as per the eligibility criteria within the GRID study.

- Compared to other cancer medicines the proportional benefit to the patient in terms of increased life expectancy and quality of life was felt to be particularly high.

Summary of ultra orphan decision making framework

Nature of the condition

Patients with unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with standard treatment options (imatinib and sunitinib) have a poor prognosis and there are limited further treatment options. Current standard of care is best supportive care with an overall survival estimate of under 12 months. The psychological impact of knowing their prognosis, combined with the physical symptoms, especially pain and extreme tiredness, has a devastating effect on the quality of life of patients and their families.

Impact of the new technology
There are no other licensed treatments available for patients who have not responded to imatinib and sunitinib and the only other option available would be best supportive care or imatinib rechallenge. Data from the GRID study shows that regorafenib gave patients a median of an additional 3.9 months of disease stabilisation compared with placebo. It may lead to a decrease in tumour volume for extended periods, which in turn decreases symptoms such as pain, tiredness and shortness of breath and so makes life tolerable. Regorafenib has been shown to be associated with 17.4 months median overall survival.

Value for money
The submitting company presented a cost-utility analysis of regorafenib compared to best supportive care (BSC) in patients with unresectable or metastatic GIST who progress on or are intolerant of treatment with imatinib and sunitinib. A 3 state Markov model (progression-free, progressed and death) was used with a lifetime time horizon of 30 years. Imatinib re-treatment was not included as a comparator on the grounds that this has been not recommended as a 3rd line treatment in NICE STA guidance TA 209, 2010.

The clinical data used were from the GRID study, with the placebo arm used as a proxy for BSC. PFS and overall survival (OS) were extrapolated by fitting parametric functions to the end of the observed data: the log-normal function was selected for PFS and the exponential for OS. As there was also substantial cross-over of patients at data-cut off for the primary PFS analysis, statistical adjustment for this bias was performed using the iterative parameter estimation (IPE) method in the base case, and also the rank-preserving structural failure time (RPSFT) model in a scenario analysis.

Base case utility estimates for the progression-free and progressed disease states (0.74 and 0.68 respectively) were derived from a repeated measures analysis of EQ-5D data collected in the GRID study. The probability of grade 3 or 4 adverse events with ≥3% incidence in regorafenib patients from the GRID study was included in the model; these were hypertension, hand-foot skin reaction, and diarrhoea. However, the utility impact of these events was not assessed.

Regorafenib drug acquisition costs were estimated. The mean dose of regorafenib assumed in the model of 139.8mg/day was based on that observed in the GRID trial. Health care resource use for patient monitoring and tests, disease state resource use, end of life care and management of the grade 3 and 4 adverse events were based on a resource use survey of 15 clinicians from England and Wales, with Scottish unit costs applied. Medicines costs for palliative pain management were also included.

A PAS was submitted for regorafenib and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS offered a confidential discount on the list price of the medicine. With the PAS, the incremental cost-effectiveness ratio (ICER) for regorafenib versus. BSC was estimated to be £31,200 per quality adjusted life year (QALY) gained, based on incremental cost of £19,954, incremental life years gained of 0.90 (or 10.8 months) and incremental QALYs of 0.64. The cost difference was driven by the additional drug costs for regorafenib, with lower incremental costs associated with disease management and treatment related adverse event management.

Scenario analysis performed demonstrated that the ICER was sensitive to the choice of parametric function selected to extrapolate estimates of overall survival (OS) in the model. Use of the Weibull function resulted in an estimated survival benefit of 5.3 months rather than the 10.8 months in the base case, QALYs gained of 0.33, and an ICER of £57,336/QALY with PAS. The ICER was also sensitive to a time horizon of less than 10 years. When 5 years was applied, the ICER was estimated to be £40.9k/QALY in the base case. However, when the Weibull function was used for OS

extrapolation, the ICER did not change significantly with shorter time horizons due to all patients being estimated to have died before 10 years.

The main limitations with the economic analysis were as follows:

- A comparison was not made with imatinib re-treatment as a third-line option, which according to SMC clinical expert opinion is being used in clinical practice (the company estimated that 8.3% of eligible patients receive imatinib retreatment, based on a clinical survey conducted in England and Wales). In response to a request, the company provided an indirect comparison and economic analysis versus imatinib re-treatment that indicates an ICER in the region of £40k/QALY. However, the indirect comparison has limitations and thus it is not possible to make a robust estimate of the cost-effectiveness against this comparator.
- The clinical data used for assessment of OS were immature, based on small numbers of events and associated with high cross-over bias. Although this was adjusted using statistical methods, it was noted that more mature OS data from GRID had become available. The company subsequently provided an analysis using the mature data and accounting for cross-over which indicated improved mean survival benefits for regorafenib versus BSC compared to the interim OS data, with estimated ICERs of £25k/QALY and £27k/QALY with exponential and Weibull extrapolation of the data respectively. The analysis using these more mature data produced a much better visual fit to the observed survival data and hence seemed relatively robust. There remains a degree of uncertainty in these results, with sensitivity analysis varying the OS estimates by 95% CIs producing an ICER range of £19k-62k/QALY with exponential extrapolation, and £8k/QALY to regorafenib dominated by BSC with Weibull extrapolation.
- A time horizon of 30 years lacks plausibility given the advanced stage of disease, and is unnecessary with the application of the Weibull or exponential function for extrapolation of the mature OS data. With these functions, a 10 year time horizon makes virtually no difference to the ICER and so is a more appropriate duration. The company provided an alternative base case analysis using the log-logistic function for OS extrapolation based on this being the best statistical fit to the mature OS data. This resulted in an estimated ICER of £22.5k per QALY with the PAS. However, this function was associated with a long tail and projected survival for some patients up to 30 years which lacks plausibility.
- No post third line therapy treatment costs were considered in the base case. In the GRID study, some patients received regorafenib post progression. It is appropriate to include these costs and when this was done, the ICERs increased by approximately £3k versus BSC based on the analysis using the mature OS data.
- There were limitations in the availability of EQ- 5D data to assess post progression utility and the value of 0.68 used in the base case is high for this state. In addition, as the EQ-5D estimates for the progression-free state are not treatment-specific, disutility associated with additional adverse events related to regorafenib does not appear to have been taken into account. Hence, the ICERs comparing to BSC are likely to have been underestimated, although only by a modest amount.

Patient and Clinician Engagement

A Patient and Clinician Engagement (PACE) meeting was held for this submission. Participants indicated a range of potential impacts of the new technology for the patient. It was noted that regorafenib may offer a treatment with considerable extension of good quality life and thus patients who respond to regorafenib can maintain a relatively normal life and can even continue to work full-time as side effects are relatively manageable. This can allow patients to remain independent and contribute to family life and wider society. It was noted that this is an oral treatment administered in an outpatient setting and the side-effect profile was considered manageable.

Costs to NHS and Personal Social Services
The submitting company has estimated that between 1 and 4 patients would be treated with regorafenib per year and that this would be associated with a net drug budget impact of £30k to £74k without PAS per year. The submitting company did not estimate any costs outside of the NHS.

Impact beyond direct health benefits and on specialist services
At the PACE meeting, attention was drawn to the possible benefits of patients being able to return to work and actively contribute to society and family life through having better quality of life. As some patients may be young and have family commitments, successful treatment can provide benefits to their partner and any children. It was noted that the potential for disease to be managed could give an invaluable psychological boost to patients and their families.

The Committee considered the benefits of regorafenib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that criteria for two were satisfied: a substantial improvement in quality of life, and the absence of other treatments of proven benefit. In addition, as regorafenib is considered an ultra-orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted regorafenib for use in NHS Scotland.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Sarcoma UK and GIST Support UK, both registered charities.
- Both charities have received pharmaceutical company funding in the past two years but neither has received any from the submitting company.
- The psychological distress associated with being diagnosed with a metastatic or unresectable gastrointestinal stromal tumour (GIST), which is a rare and often terminal cancer, can be devastating for patients and their families. This combined with the physical symptoms which can include profound tiredness, anaemia, shortness of breath and pain can make it very difficult for patients to carry on family life as normal.
- Patients who develop a resistance to imatinib and sunitinib or whose cancer continues to progress currently have no further line of hope.
- Regorafenib may succeed in stabilising or controlling the progression of the GIST with resultant improvement in patients' ability to maintain an independent life-style. As regorafenib is an oral medication which can be taken at home, it is convenient for patients and their carers. Access to it would also likely help relieve the psychological distress that patients and their families have when diagnosed as it would provide them with another treatment option and further hope.

Additional information: guidelines and protocols

The European Society of Medical Oncology (ESMO) updated its clinical practice guidelines for GIST in 2014.[1] The median age of patients is between 60 and 65 years. Standard treatment of proven GIST is surgical excision. Prognostic factors in patients with GIST include: tumour site (small bowel and rectal GISTs have a worse prognosis compared with gastric GISTs), tumour size and mitotic rate. The Armed Forces Institute of Pathology risk classification system is a widely used tool. In locally advanced inoperable and metastatic disease, imatinib is the standard first-line treatment, continued indefinitely. Upon progression with imatinib, or intolerance, standard second-line treatment is sunitinib. The guideline recommends that, on the basis of the GRID study results, when regorafenib becomes routinely available it should be considered the standard third-line option for patients progressing or failing to respond to imatinib and sunitinib. Participation in clinical trials should be considered for patients with metastases. Patients who develop progressive disease on tyrosine kinase inhibitors may benefit with continuation or re-challenge, if no other option is available at the time. Evidence suggests continuation may slow down the rate of progression and patients who have been re-challenged with imatinib have benefited from this strategy.

Scottish guidelines for the management of GIST were published in 2010 and clinical management guidelines updated in 2013.[2,7] In patients who progress with imatinib, the treatment approach should be discussed and decided on an individualised basis by the multi-disciplinary team. Options include: surgery, radiofrequency ablation, or a switch to sunitinib. Patients who progress with sunitinib should be considered for participation in clinical trials, or in the absence of a suitable study, imatinib may be reintroduced for symptomatic relief.

Additional information: comparators

There are no treatments specifically licensed for use third-line following imatinib and sunitinib. Imatinib re-challenge is recommended by Scottish guidelines for symptomatic relief in the absence of any suitable clinical study.

Cost of relevant comparators

Drug	Dose Regimen	Cost per four week cycle (£)	Cost per year (£)
Regorafenib	**160mg orally once daily for first three weeks in a four week cycle**	**3,744**	**48,672**
Imatinib	400mg orally once daily	1,609	20,923

Doses are for general comparison and do not imply therapeutic equivalence. Cost of imatinib from eVadis on 03 Nov 2014 and regorafenib from www.mims.co.uk on 19 Nov 14.

Additional information: budget impact

The submitting company estimated there to be 9 patients each year eligible for treatment with regorafenib with an estimated uptake rate of 20% of patients in year 1 (2 patients), 35% in year 2 (3 patients), and 50% of patients in year 5 (5 patients).

Without PAS, the submitting company estimated the gross medicines budget impact to be £30k in year 1 and £74k in year 5. Some use of third line imatinib retreatment was assumed, with all assumed to be displaced by regorafenib resulting in a net medicines budget impact of £29k in year 1 and £73k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.

1. The ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2014; 25 (supplement 3): iii21-6.
2. Reid R, O'Dwyer P, MacDuff E et al. Guidelines for the management of gastrointestinal stromal tumours (GIST) in Scotland. http://www.pathology.scot.nhs.uk/download/sgpg/guidelines/gist.pdf [Accessed 17 November 2014]
3. Bayer plc. Summary of product characteristics: Stivarga 40mg film-coated tablets. www.medicines.org.uk [Last updated July 2014]
4. Demetri GD, Reichardt P, Kang YK et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 295-302 (plus online appendix)
5. European Medicines Agency. CHMP extension of indication variation assessment report: Stivarga. Procedure no. EMEA/H/C/002573/II/0001. 26 June 2014. www.ema.europa.eu
6. Demetri GD, van Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006; 368: 1329-38.
7. Scottish Sarcoma Network. Clinical management guideline (CMG) for gastrointestinal stromal tumour (GIST) v2.0. http://www.ssn.scot.nhs.uk/index.php/guidelines [Last updated May 2013]

This assessment is based on data submitted by the applicant company up to and including 09 January 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will

be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.