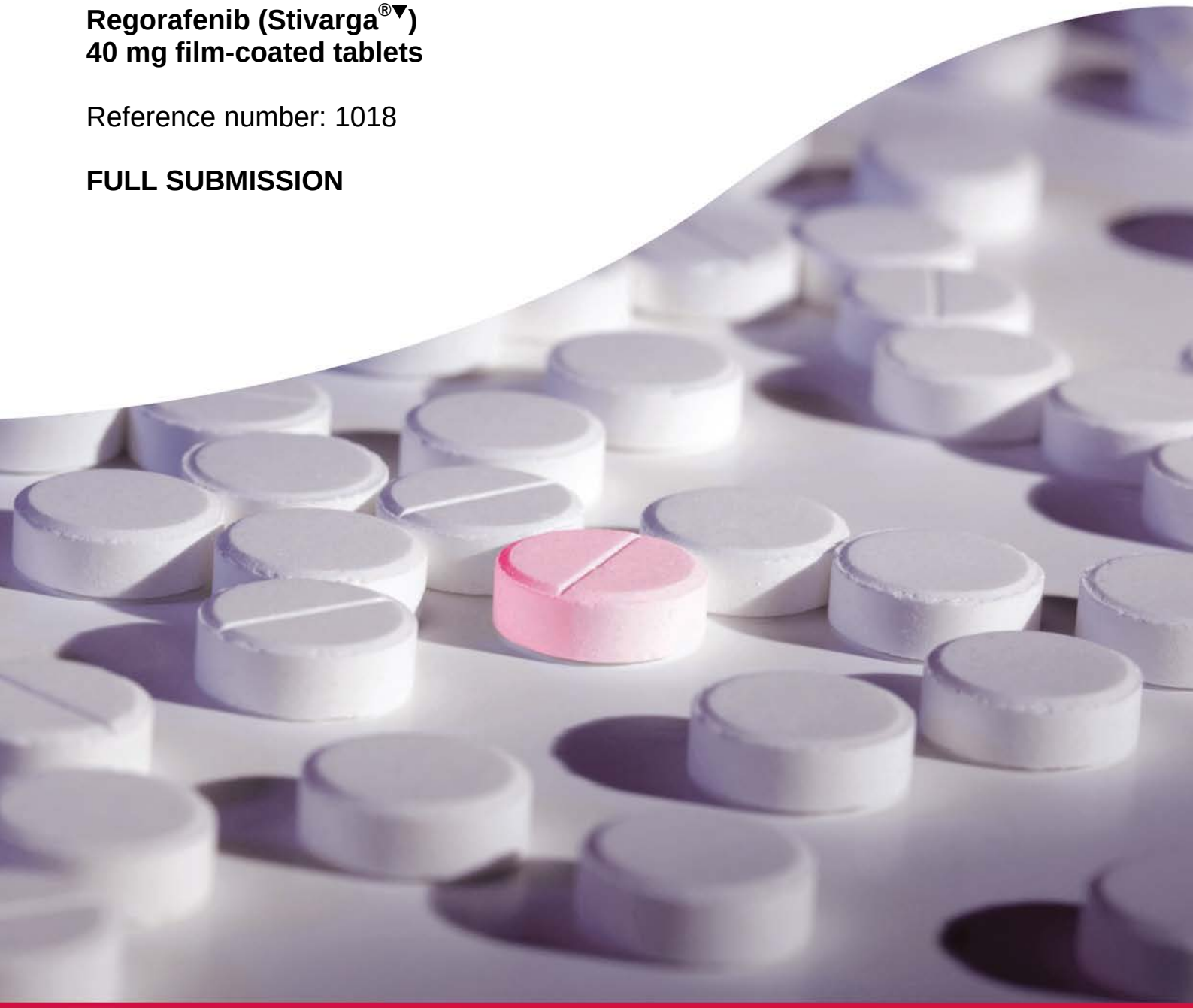
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Regorafenib (Stivarga®▼)
40 mg film-coated tablets

Reference number: 1018

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Regorafenib (Stivarga®▼) 40 mg film-coated tablets

This assessment report is based on evidence submitted by Bayer Healthcare Pharmaceuticals on 3 February 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Regorafenib (Stivarga®▼) 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. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2].
Dosing	The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily, at the same time each day, for three weeks followed by one week off therapy. This four-week period is considered a treatment cycle. Refer to the SPC for further information regarding monitoring of patients and dose modifications[2].
Marketing authorisation date	28 July 2014[3] (licensed on 26 August 2013 for the treatment of patients with metastatic colorectal cancer [mCRC] who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy[2]).

2.0 DECISION CONTEXT

2.1 Background

Gastrointestinal stromal tumours (GIST) are rare mesenchymal tumours of the gastrointestinal (GI) tract[4], affecting an estimated 13 people per 100,000 in Europe[5], with approximately 900 new diagnoses made in the UK each year[6]. GIST can occur anywhere along the GI tract but the majority (60–70%) arise in the stomach[6]. The most frequent symptoms of GIST at presentation are haemorrhage followed by abdominal pain and/or discomfort. Aggressive GIST metastasize in other locations in the abdomen, the liver and only rarely to the lymph nodes[7].

Surgical resection is the first-line intervention for patients presenting with localised primary GIST; however, post-operative recurrence or metastasis occurs in 40% to 90% of GIST patients within five years[8]. Approximately 80% of all GIST contain a mutation in the KIT receptor tyrosine kinase that results in constitutive activation of the protein[9]. The National Institute for Health and Care Excellence (NICE) recommends imatinib (Glivec®▼) at 400 mg/day as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST[6,10,11], then sunitinib (Sutent®) at 50 mg/day after failure of imatinib treatment due to resistance or intolerance[10,12]. There are currently no recommended treatments for adults with unresectable or metastatic GIST who have progressed on or are intolerant to prior treatment with imatinib and sunitinib[1,13]. Regorafenib (Stivarga®▼) is a novel, oral inhibitor of several protein kinases, including mutated KIT[1,2,13], licensed in the UK for use in this patient population[2].

2.2 Comparators
The comparator included in the company submission was best supportive care (BSC).

2.3 Guidance and related advice
- NICE. Gastrointestinal cancers pathway (2015)[10].
- European Society for Medical Oncology (ESMO)/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2014)[14].
- National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN guidelines®). Soft tissue sarcoma (2013)[15].
- NICE. Technological Appraisal (TA) 209. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (2010)[6] (partial update of NICE TA86 [2004][11]).
- NCCN. NCCN task force report: update on the management of patients with gastrointestinal stromal tumours (2010)[16].
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland. Guidelines for the management of gastrointestinal stromal tumours (GIST) (2009)[17].

In February 2014, the All Wales Medicines Strategy Group (AWMSG) issued a Statement of Advice due to non submission for the use of regorafenib (Stivarga®▼) for the treatment of adult patients with metastatic colorectal cancer who have been previously treated with, or are not considered candidates for, available therapies[18].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of one phase III pivotal study (GRID) evaluating the efficacy and safety of regorafenib by comparing regorafenib plus BSC versus placebo plus BSC[1].

3.1. GRID study[13]
This study was an international, multi-centre, randomised, placebo-controlled study in adult patients (age ≥ 18 years) with metastatic and/or unresectable GIST who failed on imatinib (defined as disease progression or intolerance), and sunitinib (defined as disease progression only)[1,7,13]. A total of 199 patients were randomised (2:1) to enter the double-blind phase to receive either regorafenib or matching placebo, 160 mg (4 x 40 mg once daily), for three weeks, followed by one week off therapy[1,7,13]. All patients additionally received BSC (defined as any method to preserve the comfort and dignity of the patient, excluding disease-specific anti-neoplastic therapy, such as tyrosine-kinase therapy other than study treatment, chemotherapy, radiation therapy, or surgical intervention)[1,13]. Patients were treated until disease progression, unacceptable toxicity, and/or study withdrawal. Patients assessed as having progressive disease had the option of entering an open-label phase and receiving treatment with regorafenib irrespective of the randomised treatment received[1,7,13]. All patients were followed from survival until death, except for those who specifically did not consent to long-term follow-up[1].

The primary endpoint was progression-free survival (PFS), defined as the time from randomisation to the date of first observed radiological progression per blinded central radiology review, or death due to any cause, if death occurred before progression[1,7]. Primary and secondary endpoints are presented in Table 1. At the pre-defined criteria of 144 events (72.4%), there was a statistically significant improvement in PFS in the regorafenib arm compared with the placebo arm, with a gain in median PFS of 119 days[1,7,13]. The robustness of the PFS effect was supported by sensitivity analyses[1,7]. The effect was further substantiated by results from secondary endpoints. No

significant difference was observed between regorafenib and placebo in terms of overall survival (OS)[7].

Exploratory endpoints included health-related quality of life (HRQoL) which was evaluated with European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and European Quality of Life-5 Dimensions (EQ-5D) questionnaires, and secondary PFS (time from first progression until second progression or death) during or after the open-label phase[1,7]. Mean changes in HRQoL scores from baseline were, overall, similar between the regorafenib plus BSC and placebo plus BSC groups; suggesting no remarkable difference between the two study arms regarding quality of life[1,7]. Median secondary PFS in the placebo arm and regorafenib arm was 151 days and 137 days, respectively[1,7].

Table 1. Overview of primary and secondary endpoints from the GRID study[7,13].

		Regorafenib + BSC	Placebo + BSC
Primary endpoint			
PFS*	Patients randomised	133	66
	Number of patients with progressive disease or died (%)	81 (60.9)	63 (95.5)
	Number of patients censored (%)	52 (39.1)	3 (4.5)
	Median, days (95% CI)	147 (122 to 173)	28 (28 to 32)
	Log-rank p-value (stratified)	< 0.000001	
	Hazard ratio (95% CI)	0.268 (0.185 to 0.388)	
Secondary endpoints			
OS: preliminary analysis*†	Number of patients with event (%)	29 (21.8)	17 (25.8)
	Number of patients censored (%)	104 (78.2)	49 (74.2)
	Median, days (95% CI)	NR§	NR§
	Log-rank p-value	0.199	
	Hazard ratio (95% CI)	0.772 (0.423 to 1.408)	
OS: follow-up analysis¶	Number of patients with event (%)	91 (68.4)	48 (72.7)
	Median, days (95% CI)	529 (373 to 640)	529 (454 to 614)
	Log-rank p-value	0.180	
	Hazard ratio (95% CI)	0.85 (0.597 to 1.206)	
TTP	Median, days (95% CI)	165 (125 to 174)	28 (28 to 34)
	Log-rank p-value	< 0.000001	
	Hazard ratio (95% CI)	0.248 (0.170 to 0.364)	
DCR	Percentage of patients with CR, PR or stable disease (95% CI)	52.6 (NR)	9.1 (NR)
	Log-rank p-value	< 0.000001	
	Hazard ratio (95% CI)	−54.72 to −32.49	
DOR	Median, days (95% CI)	99 (NR)	30 (NR)
ORR	Percentage of patients with CR or PR (95% CI)	4.5 (1.7 to 9.6)	1.5 (0.0 to 8.2)
	Log-rank p-value	0.142097	

*****Analysis conducted 26 January 2012.
†Uncorrected for the effect of cross-over from the placebo to the regorafenib arm.
§Value cannot be estimated due to censored data.
¶Analysis conducted at follow-up stage, 31 January 2014.

BSC: best supportive care; CI: confidence interval; CR: complete response; DCR: disease control rate (percentage of patients with CR, PR or stable disease); DOR: duration of response (number of days from PR or CR to disease progression or death); NR: not reported; ORR: overall tumour response rate (percentage of patients with CR or PR according to Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria); OS: overall survival (time from randomisation to death due to any cause); PFS: progression-free survival; PR: partial response; TTP: time to progression (time from randomisation to radiological progression).

3.2 Comparative safety

Evidence of the safety and tolerability of regorafenib plus BSC, when compared to placebo plus BSC, was provided by safety analyses and adverse event (AE) reporting from the GRID study[1]. According to the inclusion criteria, patients were required to have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (0 = normal activity, 1 = some symptoms, but still near fully ambulatory)[19], and adequate bone marrow, renal and hepatic functions. Results relate to the study up until the primary analyses cut-off and include 198 patients who had received at least one dose of study medication (regorafenib, n = 132; placebo, n = 66)[1,7,13].

Overall, the safety profile of regorafenib was typical for an angiogenetic and multi-tyrosine-kinase inhibitor: no new AEs were reported in the GRID study[1,7]. During the double-blind period, all patients in the regorafenib group and 92% in the placebo group had AEs[7,13]. Treatment-related AEs (TAEs) were reported in 98% of patients in the regorafenib group and 68% in the placebo group. The most common AE of any grade was hand-foot skin reaction (regorafenib: 56%; placebo 14%)[1,13]. TAEs of grade 3 or higher were reported in 61% of patients in the regorafenib group and 14% in the placebo group. The most common regorafenib-related AEs of grade 3 or higher were hypertension (23%), hand-foot skin reaction (20%), and diarrhoea (5%). Serious AEs (SAEs) were reported in 29% of patients in the regorafenib group and 21% in the placebo group. The most common SAEs in the regorafenib group were abdominal pain (4%), fever (2%), and dehydration (2%); whilst in the placebo group, the most common SAEs were fatigue (3%) and pain (3%)[1,13].

During the double-blind phase, the mean daily doses of regorafenib and placebo were 146.8 mg (range 88–160) and 160 mg (139–160), respectively[7,13]. Although dose modifications during the double-blind treatment period were more frequent in the regorafenib group (72% of patients versus 26% in the placebo group), the occurrence of AEs that led to permanent discontinuation of treatment was similar between the groups (6% of patients in the regorafenib group versus 8% in the placebo group), suggesting that in most cases, AEs were manageable by dose modification without the need to discontinue treatment[7,13]. Death was reported in seven (5%) patients in the regorafenib arm and three (5%) patients in the placebo arm; of these two in the regorafenib and one in the placebo group were deemed treatment-related[1,7,13].

3.3 AWTTC critique

- Currently, there are no standard treatment options in the European Union for adult patients with unresectable or metastatic GIST who have progressed on or are intolerant to prior treatment with imatinib and sunitinib[1,7]. Regorafenib is the only licensed treatment for this patient population[1].
- The two-arm design of the GRID study, with placebo plus BSC as the comparator, was considered acceptable by the Committee for Medicinal Products for Human Use (CHMP), as patients enrolled in the trial had received all the standard treatment options currently available[7].
- CHMP reported that the treatment comparison is biased by the large cross-over of patients from the placebo arm to the regorafenib arm (84.8%). The observed median OS (17.4 months) in the GRID study was long compared to other studies in GIST patients after failure of at least imatinib and sunitinib, where a median OS of less than 12 months is usually reported[7]. Despite this, there was a 23% relative risk reduction of death in the patients receiving regorafenib compared with those receiving placebo[1].
- Efficacy of regorafenib based on PFS was identified in nearly all subgroups (geographic region, prior line of treatment, age, sex, baseline body-mass index [BMI], duration of imatinib treatment, ECOG performance status, and mutational status), except for the small subset of patients (n = 22) with a duration of imatinib treatment of less than six months[1,13].

- In the GRID study, median duration of the safety follow-up of patients is relatively short and long-term safety data are currently not available[7]. An updated safety analysis will be provided in the next 6–12 months when final OS data becomes available. The additional information to be provided is in the risk management plan[7].
- The GRID study is currently the only phase III study conducted to evaluate the efficacy and safety of regorafenib for GIST; therefore, the company were unable to provide a systematic review or meta-analysis in their submission[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company has submitted a cost-utility analysis of regorafenib compared to BSC in patients with unresectable or metastatic GIST who progressed on, or are intolerant to, prior treatment with imatinib and sunitinib. A Markov model was used consisting of three health states (progression-free, progression and death), 28-day cycles, and a lifetime time horizon of 30 years. The cohort in the model had a start age of 60 years.

The clinical data for the economic analysis was from the GRID study, with patient level intention-to-treat data used for PFS at the primary analysis and OS data taken from the follow-up analysis[13]. The placebo arm of GRID was used as a proxy for BSC. PFS and OS data were extrapolated by fitting parametric functions to the end of the observed data, with in the base case the choice based on best statistical goodness of fit. The log-normal function was used for PFS, and a log-logistic function for OS. The use of alternative parametric functions was explored in scenario analysis. There was significant cross-over of patients from placebo to regorafenib at the 2012 data-cut off for the primary PFS analysis (84%), hence statistical adjustment was performed using the iterative parameter estimation (IPE) method. This method was selected in the base case on the grounds that it had performed well relative to other cross-over bias adjustment methods in reducing bias in estimates of true treatment effect in a published simulation exercise[20]. In scenario analysis an alternative method, the rank preserving structural failure time (RPSFT) model approach, was used.

Health state utility estimates used in the base case were derived from a repeated measures analysis of EQ-5D data collected in the GRID study, and were estimated to be 0.744, 0.707 and 0.681 for progression-free, at progression, and progressed respectively.

The treatment acquisition cost used in the base case for regorafenib at list price (£44.57 per 40 mg tablet) was based on a mean dose observed in the GRID trial of 139.8 mg/day. This is less than the recommended daily dose of regorafenib of 160 mg, resulting in an estimated cost of £3,271 per four-week treatment cycle (three weeks on treatment and one week off). A Wales Patient Access Scheme (WPAS) [commercial in confidence information removed]. The costs of regorafenib treatment used post-progression in the GRID trial was not included in the base case.

Health care resource use estimates for patient monitoring and tests, disease state resource use, end-of-life care and management of the grade three and four AEs with ≥ 3% incidence in regorafenib patients from the GRID study (hypertension, hand-foot skin reaction, and diarrhoea) were obtained from a survey conducted in 2013 of 14 GIST medical oncologists from England and one from Wales. Unit costs were derived primarily from the British National Formulary (BNF) for treatment costs and NHS reference costs 2012–2013 for resource use.

4.1.2 Results

The estimated incremental cost per quality-adjusted life year (QALY) gained for the base case comparison of regorafenib versus BSC, taking into account the WPAS, is £19,695. This is based on incremental costs of [commercial in confidence figure removed] and incremental QALYs of 1.01 (Table 2). The main driver of the results is the additional treatment acquisition costs of regorafenib, and some additional monitoring and AE management costs. Life years gained of 1.43 were estimated, with 68% of the survival benefit predicted to be obtained post-progression. Without the WPAS, the incremental cost-effectiveness ratio (ICER) was estimated to be [commercial in confidence figure removed] gained based on an incremental cost of [commercial in confidence figure removed].

Table 2. Base case analysis results (with WPAS)*.

	Regorafenib	BSC	Increment
Treatment costs	¶¶	¶¶	¶¶
Other costs†	¶¶	¶¶	¶¶
Total costs	¶¶	¶¶	¶¶
Progression-free life years gained	0.57	0.11	0.46
Total life years gained	2.68	1.25	1.43
QALYs gained	1.86	0.86	1.01
ICER (deterministic)			£19,695

*Costs and benefits discounted at 3.5%.
†These cover adverse event, monitoring and end-of-life care costs.
¶¶Commercial in confidence data removed.

BSC: best supportive care; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years; WPAS: Wales Patient Access Scheme.

Table 3 presents results for the most sensitive and/or plausible alternative scenarios. The results were sensitive to the choice of parametric function selected to extrapolate estimates of OS in the model, but not to the use of the alternative RPSFT method for adjusting for cross-over bias, or to alternative methods of analysing EQ-5D data to estimate health state utilities. Reducing the time horizon to five years increased the ICER to £28,481/QALY. Including post-progression regorafenib treatment costs increased the ICER (Table 3).

Probabilistic sensitivity analysis based on 3,000 simulations indicated a 99.8% probability of regorafenib being cost-effective at a threshold of £30,000/QALY.

Table 3: Selected scenario/sensitivity analyses.

Sensitivity analysis	Incremental cost	Incremental LYG	Incremental QALY	ICER	Plausibility
Weibull function fitted to end of observed data to estimate OS	£19,211	1.05	0.74	£25,879	This appears to be potentially more clinically plausible parametric function as there is a long tail associated with the base case log logistic function (i.e. 94% of regorafenib patients had died by 10 years in the model with this function, but at 30 years there were still 1.2% regorafenib patients estimated to still be alive. With the Weibull function, it appears from the model that almost all patients had died by 10 years, which is maybe more plausible clinically.
PFS extrapolation performed fully parametrically	£24,685	1.43	1.01	£24,374	There is some upward uncertainty in the ICER for PFS extrapolation based on full parametric function fitting. As plausible as extrapolating from end of trial.
RPSFT method used to adjust for cross-over bias	£19,744	1.40	0.98	£20,116	The RPSFT is the relatively more used method in HTA submissions, and results in lower estimates of survival gain. It may have been preferable to have used this in the base case.
Time horizon five years	£18,417	0.91	0.65	£28,481	This time horizon is potentially too short to be a plausible base case.
Time horizon 10 years	£19,290	1.20	0.84	£22,893	This is a more plausible time horizon than the base case 30 years which is very long for such an advanced stage of cancer, with poor prognosis. This is associated with the long tail estimated by the base case log-logistic OS extrapolation (see above).
Lower utility for the progressed disease state (0.647 based on alternative method of EQ-5D analysis)*	£19,791	1.43	0.97	£20,365	This utility for progressed disease may have greater face validity than the 0.68 in the base case.
Inclusion of post-progression regorafenib costs	£21,609	1.43	1.01	£21,505	As the outcomes are associated with post-progression use in the trial, then these costs should be included, hence should be included in the base case.
Full regorafenib daily dose of 160 mg	£22,284	1.43	1.01	£22,176	This is the recommended dose and provides an upper estimate associated with dose uncertainty, but not more plausible than the base case.
Scenario of 10 year time horizon, Weibull OS, include regorafenib post-progression costs, RPSFT cross-over adjustment	£20,907	1.01	0.72	£29,055	This scenario can be considered as an alternative potentially more plausible base case than that presented, based on comments above. As an indicator of uncertainty in this estimate an analysis whereby the 95% CI's for the placebo HR for OS are applied produces an ICER range of £22,618–£38,644/QALY gained.
Above multi scenario + full parametric PFS + OS	£25,711	1.06	0.76	£33,876	The alternative base case above including using a fully parametric approach to extrapolation rather than to the end of trial data. As an indicator of uncertainty in this estimate an analysis whereby the 95% CI's for the placebo HR for OS are applied produces an ICER range of £28,586–£50,687/QALY gained.

HTA: health technology assessment; ICER: incremental cost-effectiveness ratio; LYG: life years gained; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life year; RPSFT: rank preserving structural failure time model.
*Analysis based on paired sample comparisons

4.1.3 AWTTC critique

The company economic evaluation has used a standard economic model similar to other models used in the assessment of cost-effectiveness of cancer therapies, and can be considered appropriate. In general, the economic model is robust and the evaluation well performed. A particular strength of the analysis is the availability of EQ-5D data with which to estimate health state utilities, and useful range of scenario analyses that were provided.

The base case ICER is under £20,000 per QALY gained with WPAS compared with BSC alone, although some of the base case assumptions means this maybe a relatively optimistic estimate of cost-effectiveness. In particular, there is uncertainty with the survival benefits associated with regorafenib over BSC associated with the methods of extrapolation adopted, the extensive cross-over from the placebo group, hence need for statistical adjustment, the implausibly long time horizon of 30 years, and the below-recommended daily dose of regorafenib. In addition, post-progression regorafenib costs should be included as the outcomes estimated are based on including this use. Hence, an AWTTC preferred 'base case' scenario using a more plausible time horizon of 10 years, fitting a parametric function that produces potentially more plausible survival projections, using the relatively established RPSFT method for adjusting for cross-over bias, and including post-progression costs of regorafenib produces an ICER estimate of £29,055 with the WPAS (see Table 3 above). If a fully parametric PFS and OS extrapolation is performed the ICER estimate is £33,876/QALY. Applying the upper and lower 95% CI's for the placebo/BSC HR for OS with the Weibull extrapolation produces an estimated ICER range of £23,000–39,000/QALY, or a range of £22,000–51,000/QALY if fully parametric PFS and OS extrapolation is performed (Table 3).

A further limitation is that whilst AE costs have been accounted for, it is not clear that the impact of additional AEs associated with regorafenib have been taken into account (AE disutility can be captured by the EQ-5D data but this has not been analysed by treatment arm in the model in order to assess the differential impact of regorafenib AEs on QALY outcomes).

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Estimates of the incidence of GIST and the proportion of patients who were metastatic and unresectable and previously treated with imatinib and sunitinib were obtained from a previous NICE submission for sunitinib in GIST[12], and a published trial of sunitinib after imatinib failure[21]. The proportion of these patients eligible for further treatment with regorafenib was estimated at 60% based on the survey of 15 medical oncologists experienced in the treatment of GIST. This equated to approximately three patients each year eligible for regorafenib treatment. The expected number of treated patients are based on regorafenib uptake rates of 22% in year one rising each year to a maximum of 90% in each of years four and five (Table 4).

5.1.2 Results

In the base case the company has estimated the treatment cost associated with the introduction of regorafenib at £14,039 in year one rising to £58,587 in year five without WPAS applied[1]. With the WPAS applied, the treatment cost is estimated to be [commercial in confidence figure removed] in year one, rising to [commercial in confidence figure removed] in year five. There is a small increase in resource costs after account is taken of changes in monitoring and follow-up costs, AE management and end-of-life costs from the introduction of regorafenib (Table 4). Sensitivity analysis was performed around the incidence of GIST (+/− 33%), which resulted in medicines

costs varying between an estimated £9,360 to £18,719 in year one without WPAS ([commercial in confidence figure removed] with WPAS), and £39,058 to £78,115 in year five without WPAS ([commercial in confidence figure removed] with WPAS). Sensitivity analysis was also performed in which a mix of licensed and unlicensed medicines are assumed to be displaced resulting in an estimated net medicine and resource cost of £7,285 in year one and £30,402 in year five without WPAS, and [commercial in confidence figure removed] with WPAS[1].

Table 4. Company-reported base case budget impact of regorafenib.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication[s] covered in this submission)	3.22	3.24	3.26	3.27	3.28
Uptake in incident patient population (%)	22	55	89	90	90
Treated patients	0.71	1.78	2.90	2.94	2.95
Net costs					
Net costs (Medicine costs) without WPAS	£14,039	£35,380	£57,478	£58,355	£58,587
Net costs (Medicine costs) with WPAS	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine and resource cost (without WPAS)*	**£14,177**	**£36,060**	**£57,864**	**£58,672**	**£58,830**
Net medicine and resource cost (with WPAS)*	¶¶	¶¶	¶¶	¶¶	¶¶

WPAS: Wales Patient Access Scheme.
*Monitoring and follow-up costs, adverse event management costs and end-of-life costs are included and represent the undiscounted costs in the relevant year between the regorafenib + BSC arm and BSC arm in the cost-effectiveness model.
¶¶Commercial in confidence data removed.

5.1.3 AWTTC critique

- The sources used for estimating the number of patients with metastatic and unresectable GIST and previously treated with imatinib and sunitinib seem reasonable.
- The derivation of the uptake rates estimated have not been explained hence cannot be verified and are uncertain.
- Given the small numbers, more meaningful estimates would be for whole patient numbers in each year rather than a proportion of a patient.

5.2 Comparative unit costs

There are currently no recommended treatments for adults with unresectable or metastatic GIST who have progressed on or are intolerant to prior treatment with imatinib and sunitinib[1,13]. Regorafenib (160 mg orally once daily for the first three weeks in a four week cycle) would cost £3,744 per cycle (doses based on SPC[2]; cost based on BNF list price[22]).

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, regorafenib (Stivarga®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company have highlighted in their submission that regorafenib (Stivarga®▼) may be supplied by a home healthcare provider.

6.2 Ongoing studies
The company submission highlighted the GRID study as ongoing. The main data to be reported is OS and long-term safety and is likely to be available within 6–12 months[1,7].

6.3 AWMSG review
This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search
Date of evidence search: 12 February 2015
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy on life-extending, end-of-life medicines
The applicant company believe that the use of regorafenib in the given patient population meets the end-of-life criteria set by the AWMSG Policy on appraising life-extending, end-of-life medicines[23,24].

The criteria for appraising life-extending, end-of-life medicines apply when the most plausible ICER estimate exceeds £30,000 per QALY gained, and all the following conditions are satisfied:

- The medicine is indicated for patients with a short life expectancy, normally less than 24 months (e.g. estimated from the median survival of patients in the control group of the pivotal study).
- There is sufficient evidence to indicate that the medicine offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment. The estimates of the extension to life (e.g. based on the difference in median survival in the pivotal trial, or projected life-years gained) should be robust and shown (or reasonably inferred) from either progression free survival or overall survival.
- AWMSG/NMG will consider the cumulative population of each licensed indication of the medicine to be small[23].

Despite the company's base-case ICER being less than £30,000 per QALY gained, the most plausible ICER for regorafenib is in the region of £29,000–£34,000 per QALY when compared with BSC for the licensed indication under consideration, and so may exceed £30,000 per QALY gained.

An analysis of the GRID study demonstrated an estimated median OS of 17.4 months (95% CI: 12.3 to 21.1 months) in the placebo arm, which is less than the 24 months normally required. Furthermore, this estimate was without adjustment for patient cross-over and hence the OS for BSC could be even shorter.

There was no difference in median OS in the GRID trial, although this was associated with cross-over of patients from placebo to regorafenib. The company, however, believe that there is sufficient evidence that regorafenib offers an extension to life of at least three months following adjustment using RPSFT modelling to account for cross-over effects. The company reports an additional median OS advantage of 7.3 months, compared to placebo. However, no CIs are presented to judge whether this differs significantly from 3 months, or whether median OS is statistically significantly different from the 8.6 months (95% CI 6.2 to 10.2) in the placebo group. The company notes that the CIs associated with the RPSFT model treatment effect may be relatively large. In the economic analysis, the company reported the projected mean survival benefit of about one year. This was based on the most plausible base case as indicated in Table 3.

For the GIST indication under consideration, the company estimate that up to six eligible patients in Wales will have previously failed on both imatinib and sunitinib and

that of these three per year will be appropriate for treatment with regorafenib, based on clinical expert opinion[1]. However, in order for regorafenib to meet the end-of-life criteria, AWMSG/NMG would need to consider the cumulative population of each licensed indication (i.e. GIST and mCRC) of the medicine to be small.

6.6 Consideration of AWMSG policy relating to ultra-orphan medicines

The applicant company suggests that regorafenib may be considered under the AWMSG policy relating to ultra-orphan medicines[1]. For the GIST indication under consideration, as previously stated, the company estimate that up to six eligible patients in Wales will have previously failed on both imatinib and sunitinib and that of these three per year will be appropriate for treatment with regorafenib. This number is below one in 50,000.

The policy applies to medicines with orphan designation in the European Union (EU) that are licensed for the treatment of disease with a prevalence of less than one in 50,000 in the EU[25]. Regorafenib was not designed for an orphan condition and has not been given orphan status by the European Medicines Agency (EMA)[7], although consideration may be given to whether the full population of the licensed indication(s) is equal to, or less than, 5 in 10,000 persons which is consistent with the prevalence definition of an orphan medicine. There is a paucity of collected data for GIST, which means that the number of patients diagnosed each year in Wales is uncertain. Although UK registries are being developed these have not yet reported prevalence data[26,27]. The applicant company highlights a study that concludes there is a very high probability of third-line treatment-eligible GIST prevalence being below two per 100,000 population in the UK[28]. This estimate however does not consider all patients diagnosed with GIST and does not take in to consideration the fact that regorafenib is also indicated for the treatment of mCRC. Using the National Cancer Registry for Wales[29] to estimate the numbers of patients with CRC and ESMO guidelines[30] to estimate the proportions to be diagnosed metastatic or to develop metastasis in each year, there are an estimated 1,528 mCRC patients in Wales. The prevalence of mCRC alone is therefore estimated to be above the thresholds for orphan status and ultra-orphan status. AWTTC are therefore of the opinion that regorafenib does not meet the criteria for orphan or ultra-orphan status as it is licensed for the treatment of diseases (i.e. GIST and mCRC) with an estimated prevalence of more than 5 in 10,000 persons.

Should New Medicines Group (NMG)/AWMSG consider the ultra-orphan medicines policy to apply to regorafenib, the same criteria for clinical effectiveness and cost-effectiveness of ultra-orphan medicines as those applied to other medicines will be considered, but recognising that the evidence base will necessarily be weaker. NMG/AWMSG would also recognise that the ICERs of many ultra-orphan medicines will exceed the threshold cost-effectiveness range. In such cases, NMG/AWMSG will consider evidence on the following to inform their decisions (in descending order of priority)[25].

Table 6. Evidence considered by NMG/AWMSG.

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival.	The disease is clearly at an advanced stage in that patients are metastatic and unresectable, and have progressed after both imatinib and sunitinib therapy. In the GRID study patients, median survival was based on an updated survival analysis (January 2014) which demonstrated a median OS of 17.4 months in the placebo arm, but this is confounded by cross-over. Mean OS in the placebo arm after adjustment for cross-over is estimated at just 8.8–10.1 months (dependent on method of cross-over adjustment used), but indicates high severity in terms of survival prognosis. Quality of life based on GRID study data appears to be consistent with that typically seen with advanced stage cancers.
Whether the medicine can reverse, rather than stabilise the condition.	No evidence that regorafenib can reverse the condition. It does seem to offer additional months of PFS (median of 3.9 months, and projected mean PFS benefit of ~5.5 months, and survival benefits once cross-over from placebo is accounted for of around one year compared to BSC.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy), and that this "definitive" therapy is currently in development.	No evidence that regorafenib bridges to definitive treatment – the disease is at too advanced a stage.
The innovative nature of the medicine. NMG/AWMSG will consider whether the medicine: • Represents a significant improvement on existing therapy (e.g. the medicine is able to treat a condition where there was previously no effective treatment) and; • Whether it can plausibly generate substantial health gains over existing treatments for the individual (e.g. > 1 QALY).	There appears to be no other licensed therapies available, although imatinib retreatment may be an option. An indirect comparison versus imatinib retreatment has not been performed to assess relative effectiveness or cost-effectiveness of regorafenib versus imatinib retreatment using the available trial evidence. It is unlikely that regorafenib will generate QALY gains exceeding 1 QALY. With the Weibull projection, estimated QALY gains are 0.74, and with the company base case (which maybe overestimates survival gains), the QALY gain is estimated at 1.0.
AWMSG: All Wales Medicines Strategy Group; BSC: best supportive care; NMG: New Medicines Group; OS: overall survival; PFS: Progression-free survival; QALY: quality-adjusted life year.	

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