SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND
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regorafenib 40mg film-coated tablets (Stivarga®) SMC No 1316/18

Bayer plc

6 April 2018

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 assessed under the end of life process

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

Indication under review: as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib.

In a randomised, double-blind, phase III study in patients with hepatocellular cancer that had progressed on sorafenib treatment, regorafenib significantly improved overall survival compared with placebo on a background of best supportive care.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of regorafenib. This advice 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 views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Dosing Information

Regorafenib 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.

Patients with performance status (PS) of 2 or higher were excluded from clinical studies. There is limited data in patients with PS≥2.

Regorafenib should be prescribed by physicians experienced in the administration of anticancer therapy.[1]

Product availability date

August 2017.

Regorafenib meets SMC end of life criteria.

Summary of evidence on comparative efficacy

Regorafenib is an oral agent which inhibits multiple protein kinases including kinases involved in tumour angiogenesis, oncogenesis, metastases and tumour immunity.[1, 2] Regorafenib is the first medicine to be specifically licensed for second-line use in patients with hepatocellular cancer (HCC) who have been previously treated with sorafenib.[1]

The key evidence to support the use of regorafenib in HCC comes from a double-blind, randomised, phase III, RESORCE study. Eligible patients were aged ≥18 years with confirmed HCC of Barcelona Clinic Liver Cancer (BCLC) stage B or C and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria (version 1.1). They had documented radiological progression during sorafenib treatment but must have tolerated sorafenib (≥400mg daily for ≥20 of the 28 days before stopping). They had Child-Pugh A liver function and an Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1. Within 10 weeks of stopping sorafenib, they were randomised in a ratio of 2:1 to receive regorafenib (160mg) or placebo orally once daily for the first three weeks of each four week cycle. All patients also received best supportive care (BSC). Randomisation was stratified by area (Asia or rest of the world), macrovascular invasion (yes or no), extrahepatic disease (yes or no), alfa-fetoprotein concentration (<400 or ≥400 nanograms/mL) and ECOG performance status (0 or 1). If required, toxicity was managed by two regorafenib dose adjustments (from 160mg to 120mg and then 80mg daily) and treatment interruptions. Study treatment was continued until disease progression defined by modified RECIST criteria (ECOG performance status ≥3 or symptomatic deterioration including increased liver function tests), death, unacceptable toxicity, withdrawal of consent by patient, or discontinuation by physician. Study treatment could be continued after

progression if the investigator considered that this would benefit the patient. Cross-over was not allowed.

The primary outcome was overall survival, defined as the time from randomisation to death from any cause, analysed in the intention to treat population which comprised all randomised patients. At the primary analysis (cut-off date 29 February 2016), after a median follow-up of 7.0 months, 61% (233/379) of the regorafenib group and 72% (140/194) of the placebo group had died. Median overall survival was 10.6 months and 7.8 months respectively; hazard ratio (HR) 0.63 (95% confidence interval [CI]: 0.50 to 0.79), p<0.0001.[2, 3] At an updated analysis (cut-off date 23 January 2017), 77% (290/379) of the regorafenib group and 87% (169/194) of the placebo group had died. Median overall survival was 10.7 months and 7.9 months respectively; HR 0.61 (95% CI: 0.50 to 0.75), p<0.0001.[2, 4]

A number of secondary outcomes were analysed at the time of the primary analysis including progression-free survival (PFS, defined as time from randomisation to radiological or clinical disease progression [assessed by investigators] or death), time to progression (TTP, defined as time from randomisation to radiological or clinical disease progression [assessed by investigators]) and objective response rate (ORR, defined as a complete or partial response based on radiological review assessed by investigators). Secondary outcomes were assessed according to both modified RECIST and RECIST version 1.1. Regorafenib was associated with significantly greater improvements in all secondary outcomes compared with placebo.[2, 3] Results are presented in table 1.

Table 1: Results of primary and secondary outcomes of RESORCE study at primary analysis[2, 3]

	Regorafenib (n=379)	**Placebo (N=194)**	**HR (95% CI)**
Primary outcome			
Median overall survival	10.6 months	7.8 months	0.63 (0.50 to 0.79)*
Secondary outcomes			
Median PFS (mRECIST)	3.1 months	1.5 months	0.46 (0.37 to 0.56)*
Median PFS (RECIST 1.1)	3.4 months	1.5 months	0.43 (0.35 to 0.52)*
Median TTP (mRECIST)	3.2 months	1.5 months	0.44 (90.36 to 0.55)*
Median TTP (RECIST 1.1)	3.9 months	1.5 months	0.41 (0.34 to 0.51)*
ORR (mRECIST)	11% (40/379)	4.1% (8/194)	p=0.0047
ORR (RECIST 1.1)	6.6% (7/379)	2.6% (5/194)	p=0.020

HR=hazard ratio; CI=confidence interval; PFS=progression-free survival' TTP=time to progression; ORR=objective response rate; (m)RECIST=(modified) response evaluation criteria in solid tumours. *p<0.0001

Quality of life was assessed as tertiary outcomes using EQ-5D, EQ-5D VAS, Functional Assessment of Cancer Therapy (FACT)-General, FACT-Hepatobilary (FACT-Hep) and Trial Outcome Index. These assessments were performed at baseline, day one of each cycle and at the end of treatment visit. At least 80% of study patients completed questionnaires during

treatment. There were similar changes from baseline in both treatment groups in EQ-5D and FACT-Hep at the time of the primary analysis. The scores for EQ-5D and FACT-Hep using least squares mean (LSM) time-adjusted area under the curve (AUC) analysis, found numerically lower (worse) scores for regorafenib than placebo. Although the differences were statistically significant in favour of placebo for the FACT-Hep total score and Trial Outcome Index (a subscale of FACT-Hep), none of the reported differences met those considered to be minimally important differences.[2, 3]

Summary of evidence on comparative safety

In the RESORCE study, the safety profile of regorafenib was similar to that from previous studies in colorectal cancer and gastrointestinal stromal tumours and is mainly related to its mechanism of action as a tyrosine kinase inhibitor. Pancreatitis was a newly identified adverse event in HCC patients and was reported in 1.6% of patients treated with regorafenib and no patients treated with placebo.[2]

At the primary analysis, an adverse event had been reported by 100% (374/374) of patients treated with regorafenib and 93% (179/193) of patients treated with placebo and these were considered possibly related to study treatment in 93% and 52% of patients respectively. Serious adverse events were reported in similar proportions of patients in the regorafenib and placebo groups (44% and 46% respectively) but this included patients hospitalised within 30 days after last dose of study medication due to disease progression and could have confounded the result. Adverse events of ≥grade 3 severity were reported in 80% and 59% of patients respectively. Dose modifications due to adverse events occurred in 68% of regorafenib patients[2]. Permanent discontinuation due to adverse events occurred in 25% of regorafenib and 19% of placebo patients.[2, 3]

The most commonly reported adverse events in the regorafenib and placebo groups respectively included hand and foot syndrome (53% and 7.8%), diarrhoea (41% and 15%), fatigue (40% and 32%), hypertension (31% and 6.2%) and anorexia (31% and 15%).[3] The most clinically relevant grade 3 or 4 adverse events in the respective groups were hypertension (15% and 4.7%), hand-foot skin reaction (13% and 0.5%), fatigue (9.1% and 4.7%) and diarrhoea (3.2% and 0%). The incidence of hepatobilary disorders was lower in the regorafenib than placebo group (11% versus 18%). Bleeding events ≥grade 3 were reported in 5.6% of regorafenib patients and 7.8% of placebo patients.

There was a higher incidence of infections with fatal outcomes in regorafenib treated patients (1.3% compared with no patients in the placebo group) and these were mainly respiratory infections. The SPC notes that regorafenib has been associated with an increased risk of infection, some of which cases were fatal. It recommends that consideration should be given to interrupting regorafenib treatment in cases of worsening infection.[1-3]

Death, considered by the investigator to be related to study treatment, occurred in seven patients in the regorafenib group (one each due to myocardial infarction, gastric perforation, upper gastrointestinal haemorrhage, intracranial haemorrhage, encephalopathy, general or administrative site disorder and other reason) and two in the placebo group (due to hepatic failure).[3]

Since the median duration of regorafenib treatment in RESORCE was 15.6 weeks, there are limited long-term safety data.[2] In addition, the exclusion of patients who were unable to tolerate sorafenib from the RESORCE study may have reduced the incidence of adverse events to regorafenib.[3]

Summary of clinical effectiveness issues

HCC is the most common type of liver cancer and is mainly associated with known underlying risk factors including cirrhosis due to hepatitis B or C infection and alcohol use. Management depends on the stage of disease. Surgical resection, transplantation, and ablation are potential curative options at an early stage. Chemoembolisation is recommended for patients with preserved liver function and disease confined to the liver generally without vascular invasion. However, in most cases, diagnosis occurs when the disease is advanced and these curative treatments are no longer suitable. Sorafenib is licensed for the treatment of HCC and is considered the standard treatment for patients with advanced disease and well-preserved liver function and in those who have progressed following loco-regional therapy.[5-7] Sorafenib has been accepted for restricted use by SMC for patients with advanced HCC who have failed or are unsuitable for surgical or loco-regional therapies. Regorafenib is the first medicine to be licensed for the treatment of HCC in patients who have been previously treated with sorafenib. Other treatment options have failed to demonstrate a survival benefit and patients are otherwise managed by best supportive care or enrolment into a clinical study. Patients who have been previously treated with sorafenib have a poor prognosis and a median survival of seven to eight months.[2] Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area due to an absence of effective second-line treatment options. Regorafenib meets SMC end of life criteria for this indication.

The RESORCE study provides evidence of significantly improved survival compared with placebo. Although the survival benefit was small, 2.8 months, this is the first medicine to demonstrate a significant improvement in patients previously treated with sorafenib. Results of secondary outcomes also indicate significant advantages in PFS, TTP and ORR. However, the relatively low ORR (11% in the regorafenib group) suggests limited tumour shrinkage and improvements in PFS and overall survival appear to be mainly driven by disease stabilisation.[2] Disease progression and ORR were assessed both according to mRECIST and RECIST 1.1 and although results were generally similar, they were slightly higher when using mRECIST compared with RECIST 1.1 indicating that this may be more sensitive to treatment effect. Quality of life scores were statistically significantly poorer for regorafenib than placebo, but the differences were not considered clinically important. Although the study was double-blinded, there were some obvious differences in the adverse event profiles of the two treatment groups, particularly the incidence of hand and foot syndrome, which may have compromised the double-blind design.[2]

The RESORCE study population was narrower than the licensed population which may affect the 5eneralizability of the results. Study patients were required to have progressed during previous sorafenib treatment but were required to have tolerated sorafenib, therefore the efficacy of regorafenib in patients who do not tolerate sorafenib is unknown. The SPC notes that there are insufficient data for regorafenib in patients who discontinued sorafenib therapy due to sorafenib-related toxicity or only tolerated a low dose (< 400 mg daily) of sorafenib and that the tolerability of regorafenib in these patients has not been established. The RESORCE study only enrolled patients with Child-Pugh class A liver function and the efficacy and safety of regorafenib in patients with more severe liver impairment is unknown. Close monitoring of overall safety is

recommended in these patients. The overall patent population with HCC included in the RESORCE study was relatively healthy (ECOG PS=0 in 65% patients), the study excluded patients with an ECOG performance status of ≥2 therefore the efficacy and safety of regorafenib in patents with poorer performance status is also unknown. However, in clinical practice, some patients not meeting the study inclusion criteria, e.g. poorer performance status or liver function, may be considered less suitable for treatment. The European Medicines Agency has noted that the company will perform a non-interventional Post Authorisation Safety Study (PASS) to assess the safety of regorafenib in patient populations excluded from the RESORCE study including those with Child-Pugh class B, ECOG performance status of 2 and patients who had previously stopped sorafenib due to toxicity.[1-3]

A proportion of patients in the RESORCE study continued regorafenib despite disease progression. While the efficacy of treatment in these patients is uncertain, patients would not routinely continue treatment post progression in clinical practice.

Whilst a biomarker evaluation was included as a tertiary outcome in the RESORCE study, no biomolecular data were available for the majority of patients. The Committee for Medicinal Products for Human Use (CHMP) has recommended that the company submits retrospective exploratory biomarker analyses to identify biomarker candidates which might help to predict response to regorafenib.[2,8]

The introduction of regorafenib would offer a licensed treatment option for patients with HCC who have previously been treated with sorafenib and, as such, is viewed as a therapeutic advancement by SMC clinical experts. Regorafenib is administered orally with limited administration implications for the service but more frequent monitoring of liver function is required.

Patient and clinician engagement (PACE)

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 end of life medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Hepatocellular carcinoma is a very severe condition which is often diagnosed at an advanced stage when treatment options are limited. This is a distressing and hopeless condition which impacts negatively on the quality of life of patients, their family and carers.
- Regorafenib addresses an unmet need for patients who have progressed on sorafenib, providing a treatment option for patients who would otherwise be managed by best supportive care.
- Regorafenib is associated with an improvement in overall survival of approximately 3 months and although this is small, is considered clinically meaningful in patients who would otherwise have a median survival of approximately 8 months.
- Patients with HCC are often younger than patients with other types of cancer. Any survival gain for younger patients is particularly important, allowing valuable added time with families and allows the opportunity to make financial and other arrangements.
- The number of patients who have progressed on sorafenib and are fit enough to tolerate regorafenib is likely to be small.

- The tolerability of regorafenib is similar to sorafenib, physicians and patients are familiar with the adverse effect profile and consider it to be manageable.

Additional Patient and Carer Involvement
We received patient group submissions from Hepatitis Scotland and the British Liver Trust, which are both registered charities. Hepatitis Scotland has received 0.85% pharmaceutical company funding in the past two years, but not from the submitting company. The British Liver Trust has received 9.12% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both charities participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing regorafenib plus best supportive care (BSC) with BSC alone in patients with advanced HCC who have been previously treated with sorafenib. BSC consisted of symptomatic treatment (palliative care) and did not include any antineoplastic chemotherapy, hormonal therapy or immunotherapy.

A partitioned survival model was used which included three health states: progression-free survival (PFS), progressed disease, and death. A 15-year time horizon was applied in the analysis. Patients entered the model in the PFS health state where they received second-line treatment with either regorafenib plus BSC or BSC and then remained on treatment until their treatment was discontinued. On moving to the progressed disease health state, patients could continue on regorafenib in keeping with the pivotal clinical study or switch to BSC.

The clinical data were based on the RESORCE study. Parametric survival curves were used to extrapolate the study data for overall survival over the model time horizon. Goodness of fit statistics and visual fit were used to select the curve used in the economic model and, based on this, the lognormal curve was chosen. No extrapolation was needed for progression free survival as the Kaplan-Meier curves in both arms reached zero within the study follow-up period. Duration of treatment was modelled for patient cohorts before and after disease progression separately. This was calculated based on the probability that patients discontinue treatment within each health state.

Utility values were estimated by a regression analysis using the EQ-5D-3L questionnaires collected in the RESORCE study. The utility value applied to the pre-progression health state was 0.811 and for post-progression was 0.763. Disutilities due to adverse events were also included in the economic model.

Medicine acquisition costs were included in the analysis as well as health state costs associated with the underlying disease and monitoring, and adverse event costs.

A Patient Access Scheme (PAS) was proposed by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland.

In the base case analysis, regorafenib had an incremental cost-effectiveness ratio of £33,444 with PAS.

The results of selected sensitivity analysis including the PAS for regorafenib are presented below.

Table 2: Selected sensitivity analyses results

Analysis	ICERs with PAS
Time horizon (3 years)	£43,031
No dose reductions	£40,752
No post-progression treatment	£30,100
Using time to treatment discontinuation curve from the RESORCE study (worst case)	£37,721
Use the Weibull function for extrapolation of OS	£38,843
Different methods for extrapolation of OS – independent curves (worst case)	£37,044
Half cycle correction not used for regorafenib acquisition cost	£35,106
Cost of hospitalisation following progression on BSC equals to that on regorafenib	£30,918
Utility for pre-progression and post-progression health states 0.7 and 0.55, resp.	£42,377
Weibull curve to extrapolate overall survival and time to treatment discontinuation, exclude half-cycle correction for acquisition costs and use the total pre-progression costs for regorafenib for the pre-progression health state for BSC	£45,408

The main limitations included:

- The utility values used in the base case analysis appear relatively high taking into account that this is an 'end-of-life' medicine, patients having had to progress on sorafenib and having advanced HCC. The impact of using a set of lower values was explored in a scenario analysis which resulted in an ICER of £42,377 with PAS.

- In the base case analysis, the submitting company modelled the duration of treatment using assumptions to calculate the probability of treatment discontinuation instead of using the time to treatment discontinuation approach, which would have been based on the patient level data that were available. Using parametric curves to extrapolate the Kaplan-Meier time to treatment discontinuation data increased the ICERs up to £37,721 with PAS.

- The base-case time horizon of 15 years is very long given that the health gains in terms of PFS and OS are quite small, all patients had evidence of progressive disease within the study itself and there are no subsequent lines of therapy. Reducing the time horizon to 3 years increases the ICER to £43,031 with PAS.

- The company provided a combined scenario analysis which addressed a number of uncertainties in the economic model. The analysis used the Weibull curve to extrapolate overall survival and time to treatment discontinuation, excluded the half-cycle correction for regorafenib acquisition costs and used the total pre-progression costs for regorafenib in the pre-progression health state for BSC. This analysis generated an ICER of £45,408 with PAS.

The Committee also 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 a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission and the absence of other treatments of proven benefit.

After considering all the available evidence and 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.**

Additional information: guidelines and protocols

The European Association for the Study of the Liver (EASL) and the European Organisation for Research and Treatment of Cancer (EORTC) published joint clinical practice guidelines for the management of hepatocellular carcinoma in 2012.[5] Sorafenib is considered the standard systemic therapy for hepatocellular carcinoma and is indicated in patients who have Child-Pugh class A liver function and have an advanced tumour or the tumour has progressed following loco-regional therapies. No clear recommendations were made for patients with Child-Pugh class B liver function. Chemotherapy, hormonal treatment and immunotherapy are not recommended for use in hepatocellular carcinoma. There is no available second-line treatment for patients with intolerance or failure to sorafenib and best supportive care or the inclusion of patients in clinical trials is recommended.

The European Society for Medical Oncology and the European Society of Digestive Oncology published Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow up in 2012.[6] Systemic chemotherapy containing anthracyclines or cisplatin was reported to have a prospect of a 10% response rate, CAPOX [capecitabine plus oxaliplatin] or GEMOX [gemcitabine plus oxaliplatin] may have a better disease control rate but none of these treatments offer a proven survival benefit. Sorafenib is considered the standard systemic therapy for patients who have advanced HCC and well-preserved liver function and in those who have progressed following loco-regional therapy. In case of progression or intolerance to sorafenib, best supportive care is preferred or patients should be included in clinical trials.

These guidelines predate the availability of regorafenib for HCC.

Additional information: comparators

There are no specific comparators.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle (£)
Regorafenib	**160mg orally once daily for three weeks followed by one week off.**	**3,744**

Costs from eVadis on 4 December 2017. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 53 patients eligible for treatment with regorafenib rising to 66 patients in year 5 to which confidential uptake rates were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

References

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This assessment is based on data submitted by the applicant company up to and including 6 February 2018.

**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

Medicine 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 medicine 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.