Cost effectiveness of regorafenib (Stivarga®) for the treatment of adult 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, in case of KRAS wild type CRC, an anti-EGFR therapy.

The NCPE has issued a recommendation regarding the cost effectiveness of regorafenib in the treatment of adult patients with metastatic colorectal cancer (mCRC), who have been previously treated with, or are not considered candidates for, available therapies. The NCPE does not recommend regorafenib as a cost effective treatment option.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturer's (Bayer) economic dossier on the cost effectiveness of Stivarga® for this indication. The NCPE use a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits, that the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence that may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

**National Centre for Pharmacoeconomics** **June 2014**

Bayer submitted a dossier to the NCPE in February 2014, to support the use of regorafenib (Stivarga®) in adult patients with mCRC who had been previously treated with, or who were not considered candidates for available therapies. These included fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, in case of KRAS wild type CRC, an anti-EGFR therapy. Regorafenib is a multi-kinase inhibitor that inhibits tumour angiogenesis and tumour cell proliferation. Regorafenib is administered at a dosage of 160mg (four 40mg tablets), once daily for the first 21 days of each 28 day cycle. Treatment should be continued until disease progression or unacceptable toxicity occurs.

1. Clinical Effectiveness of Regorafenib

- The regorafenib licence allows for use of the drug only after all other treatment options have been expended. The relevant comparator for the pharmacoeconomic evaluation was best supportive care.
- There is one trial available to support the use of regorafenib. Study 14387 (CORRECT) was a pivotal multi-centre (114 study centres in 16 countries), randomised, double-blind, placebo-controlled phase III study comparing regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with mCRC who have progressed after standard therapy which had to include all of the following: fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS wild type). Relative to the placebo arm, the regorafenib arm demonstrated a 23% relative reduction in the immediate risk of death and 51% relative reduction in the immediate risk of disease progression or death. The absolute magnitude of the effect is limited however (difference of 1.4 months in median survival times). No improvement has been reported on symptoms and the median duration of stable disease is very short in the overall population (1.2 weeks). The toxicity related to regorafenib treatment appears to be substantial.

2. Cost Effectiveness of Regorafenib

Methods

- A cost-utility analysis was submitted by Bayer comparing regorafenib with BSC. Health benefits were measured in quality-adjusted life years (QALYs) and capture health state utilities. Costs included drug acquisition and administration and health state costs from the healthcare payer's perspective.
- A three health state Markov model was used, where patient transitions between the health states were determined by the overall survival and progression free survival functions from Study 14387 (CORRECT) over a five year time horizon.

Results

- Using the NCPE's preferred set of model inputs, total costs and QALYs of regorafenib treated patients were estimated at €20,204 and 0.496 respectively, corresponding to an additional €12,653 and 0.1 QALYs compared with best supportive care.
- This resulted in an incremental cost/QALY compared with BSC of €126,246/QALY.
- Sensitivity analyses demonstrated that the model was sensitive to the assumptions used in extrapolating the survival data, utility values used pre and post progression for both placebo and regorafenib, the cost of regorafenib and the time horizon used to model the data.
- The probability of regorafenib being cost effective at €45,000/QALY was 0%.

3. Budget Impact of Regorafenib

- The projected gross budget impact of regorafenib, based on company estimates of market share, is in excess of approximately €4million over the next 5 years. Regorafenib will not displace current therapies

and as such will be an additional cost to the existing oncology drug budget. The net budget impact is therefore likely to be similar.

## 4. Conclusion

Regorafenib is licensed for use in adult patients with mCRC who have been previously treated with, or who are not considered candidates for all available therapies. Data from the pivotal trial (Study 14387, CORRECT) show a small incremental survival benefit, no quality of life improvement and a substantial toxicity profile. Data from the cost utility analyses submitted by Bayer show that regorafenib was not a cost effective treatment option in the Irish healthcare setting. Estimates of cost effectiveness, using the NCPE's preferred set of model inputs, were considerably higher again. Following NCPE assessment of the company submission, reimbursement of regorafenib is not recommended.