



Cost effectiveness of aflibercept (Zaltrap®) in combination with FOLFIRI in the treatment of adult patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen

The NCPE has issued a recommendation regarding the cost effectiveness of aflibercept in the treatment of adult patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. The NCPE believe that when compared to alternative biological agents aflibercept may be cost saving.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturer's (Sanofi) economic dossier on the cost effectiveness of Zaltrap® in the treatment of adult patients with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen. 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, which 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 which 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.

Sanofi submitted a dossier for aflibercept on 3rd October 2013. Aflibercept is indicated in combination with FOLFIRI (irinotecan/5 fluorouracil/folinic acid) for the treatment of adult patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen. Aflibercept is administered as an intravenous (IV) infusion over 1 hour, at a recommended dose of 4mg/kg of body weight.

1. The economic evaluation compared aflibercept plus FOLFIRI with bevacizumab plus FOLFIRI as well as with FOLFIRI alone in the licensed patient population. A scenario analysis considers cetuximab and panitumumab as alternative comparators.
2. A Markov model was developed in Microsoft Excel® to model the clinical and economic outcomes. It is a three health state cancer model (progression free, progressive disease, death), where the progression free health state distinguishes between time spent on and time spent off treatment. The model cycle length is 2 weeks. The model is run over 15 years.
3. The probability of moving between health states is based on efficacy data from one comparative phase III trial (VELOUR), results of which are published in the Journal of Clinical Oncology. VELOUR is a multinational, randomized, double-blind study of aflibercept in combination with FOLFIRI (n=612) compared with FOLFIRI alone (n=614) in patients with mCRC who were previously treated with oxaliplatin-based therapy. The analysis for the economic evaluation excludes patients with prior oxaliplatin-based adjuvant therapy (10% of patients) from the intention to treat (ITT) population, as adjuvant therapy is rarely used in the Irish setting. While baseline demographics in the subgroup are balanced and the number excluded is small, the review group (RG) note that it is a post-hoc analysis and potential confounding cannot be excluded. Unless indicated otherwise, the following results reflect those of the ITT population excluding adjuvant patients (aflibercept + FOLFIRI, n=552; FOLFIRI, n=550).
4. Aflibercept showed significant improvement in overall survival (OS), the primary endpoint of the study. Median OS was 13.8 months in the aflibercept plus FOLFIRI arm versus 11.9 months in the FOLFIRI arm. A significant improvement in progression free survival (PFS) was also observed (6.8 vs. 4.5 months). In order to estimate the mean time to event, the best fitting parametric model was chosen. A weibull model informs PFS and time to treatment discontinuation. For OS, separate

log-logistic curves were fitted for each trial arm; a HR of 1 (i.e. no difference) between treatments is applied from 5 years onwards.

Overall response rate (ORR), defined as achieving either a partial or a complete response, was 20% in patients receiving aflibercept plus FOLFIRI and 11% in the FOLFIRI arm. Of these, none of the aflibercept patients had a complete response compared to 2 patients in the FOLFIRI arm. (ORR outcomes are reported for the ITT population.)

5. Adverse events led to discontinuation in 27% of patients in the aflibercept plus FOLFIRI arm compared to 12% in the control arm. Grade ≥ 3 adverse events have been reported in 84% of patients in the aflibercept arm compared to 63% in the FOLFIRI arm. Aflibercept was associated with a higher frequency of anti-VEGF class side effects as well as adverse events associated with chemotherapy. The overall toxicity of aflibercept appears significant; however, the EMA considers the benefit to outweigh the risks. Only adverse events of grade ≥ 3 were included in the analysis.
6. Unfortunately, no quality of life data was collected in the trial. An interim analysis of data collected in the aflibercept early access programme (ASQoP) estimated the mean utility for patients with stable disease (0.78) (scale (0-1)). The data was too immature to inform the progressed health state. The manufacturer conducted a study in patients in clinical practice who would be eligible for aflibercept, estimating the mean utility for patients with progressed disease (0.71). Both estimates are based on small patient numbers. A lower utility value was applied to the last 2 months of life for each patient. Utility decrements (disutility) due to adverse events were based on published literature. Disutilities associated with adverse events are assumed independent of cancer type, as mCRC specific values were not available.
7. As there are no clinical trials directly comparing biologic treatments, an indirect comparison was conducted, which detected little difference in efficacy between aflibercept and alternative biologics (bevacizumab, cetuximab, panitumumab). The indirect comparison was associated with high uncertainty and validity is limited by the existing heterogeneity among the combined trials. In the absence of further information and given the high uncertainty the RG considers it appropriate to assume equal efficacy (PFS and OS) for all biologic add-on therapies. Rates of adverse events of bevacizumab, cetuximab and panitumumab are informed by clinical trials evaluating these agents.

8. Compared to bevacizumab, treating eligible patients with aflibercept results in incremental savings of €4,638 and a QALY loss of 0.01. The RG considers the reporting of an ICER for this scenario inappropriate, since such small differences in QALYs result in very unstable ICER estimates.

Compared to FOLFIRI alone, the addition of aflibercept to FOLFIRI results in an incremental cost of €15,410 and a QALY gain of 0.24; this yields an ICER of €64,132/QALY.

9. The company presented a number of scenarios, a one way sensitivity analysis as well as a probabilistic analysis in order to explore uncertainty associated with the parameters.

The scenario analysis highlighted the uncertainty associated with alternative parametric survival functions in the comparison with FOLFIRI. ICERs ranged from €59,342/QALY to €115,345/QALY. Using the best fit curve, applying a hazard ratio of 1 from end of follow up (3 years) onwards increases the ICER to €71,473/QALY. The impact on the comparison with bevacizumab was small, as equal efficacy was assumed. Not excluding the adjuvant population increases the ICER compared to FOLFIRI alone to €71,118/QALY; no significant changes occurred for the comparison with bevacizumab. Aflibercept appeared to be cost saving compared to alternative comparators cetuximab and panitumumab.

In the comparison with bevacizumab, the most influential parameters were the drug costs, administration costs and the relative efficacy of aflibercept and bevacizumab. Aflibercept remained cheaper than bevacizumab across all options; incremental savings varying from €366 to €8,910. The most influential parameters in the comparison versus FOLFIRI alone were overall survival estimates, drug costs and utility in the progressive disease health state. The ICER varied between €48,537/QALY to €97,779/QALY.

The probabilistic analysis indicates that at a threshold of €45,000/QALY, the probability of aflibercept being cost effective compared to bevacizumab was 88%. The probability of being cost effective compared to FOLFIRI was 3.7%.

10. The manufacturer predicts a 5 year cumulative gross budget impact of €5,939,321. Subtracting the cost of treatment alternatives forgone, aflibercept is predicted to yield €2,373,916 in savings to the HSE over 5 years.

11. Aflibercept is a novel recombinant fusion protein indicated in combination with FOLFIRI for mCRC patients who have previously failed or progressed on an oxaliplatin-containing regimen. Aflibercept is likely to replace existing biologic agents rather than increase the number of patients treated with a biologic agent in combination with chemotherapy. Based on the submitted data, aflibercept can therefore be recommended as a treatment option to the HSE. One should note, that the ICER compared to FOLFIRI alone is €64,132/QALY, above the usual willingness to pay threshold. However; none of the alternative biologics have been established as cost effective treatment options.