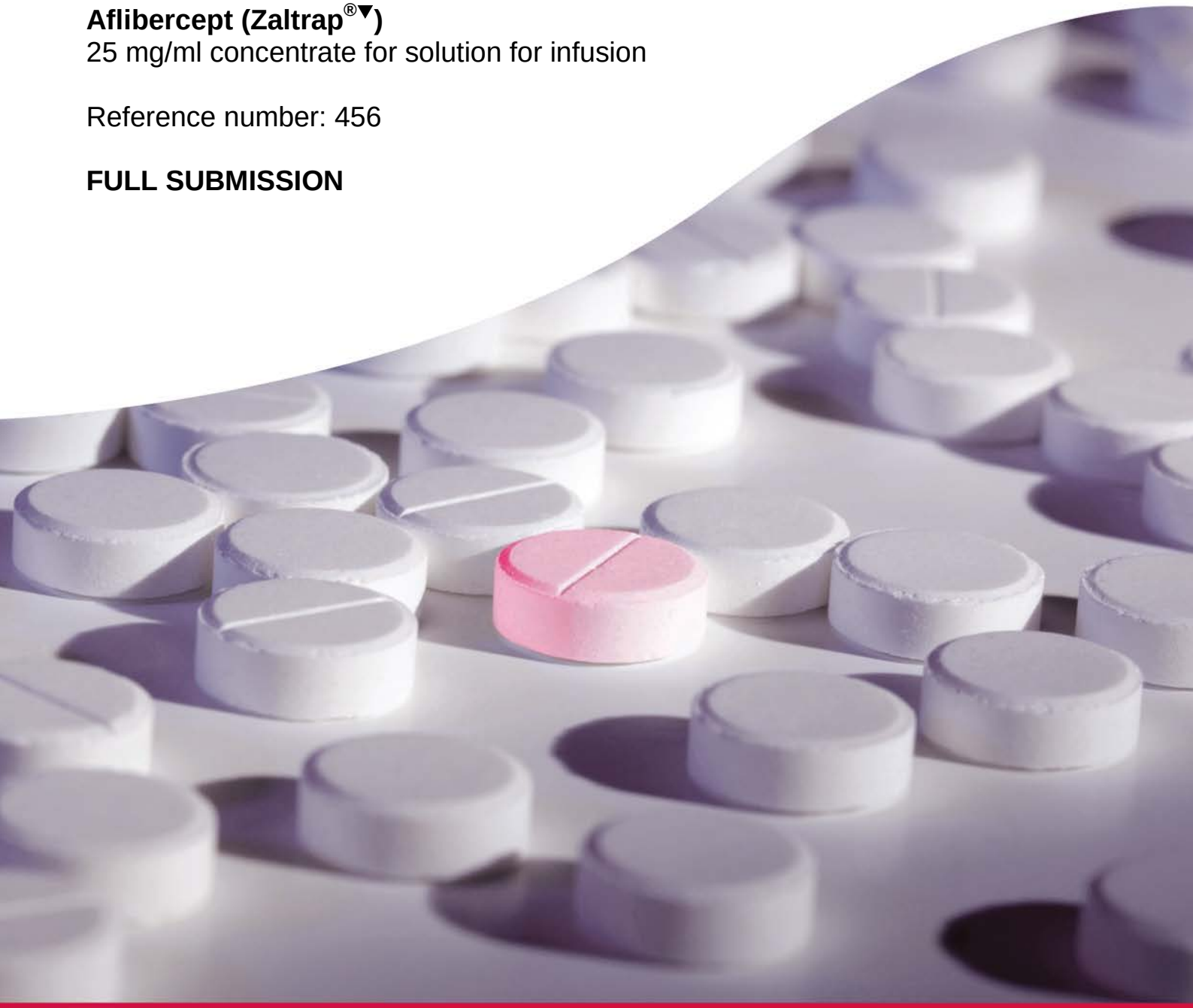
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Aflibercept (Zaltrap®▼)
25 mg/ml concentrate for solution for infusion

Reference number: 456

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

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AWMSG Secretariat Assessment Report
Aflibercept (Zaltrap®▼) 25 mg/ml concentrate for solution for infusion

This assessment report is based on evidence submitted by Sanofi-Aventis Ltd on 4 August 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Aflibercept (Zaltrap®▼) in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy is indicated in adults with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen[2].
Dosing	The recommended dose of aflibercept, administered as an intravenous infusion over one hour, is 4 mg/kg of body weight, followed by the FOLFIRI regimen. This is considered as one treatment cycle. The treatment cycle is repeated every two weeks. Aflibercept treatment should be continued until disease progression or unacceptable toxicity occurs. Refer to the Summary of Product Characteristics for further information regarding dosing[2].
Marketing authorisation date	1 February 2013[2].

2.0 DECISION CONTEXT

2.1 Background

Colorectal cancer was the third most common newly diagnosed cancer and second most common cause of cancer mortality in Wales between 2008 and 2010[3]. For patients with advanced or metastatic colorectal cancer (mCRC), the National Institute for Health and Care Excellence (NICE) Clinical Guidelines (CG) recommends chemotherapy regimens oxaliplatin/5-fluorouracil/folinic acid (FOLFOX) first-line followed by second-line treatment options, single-agent irinotecan or irinotecan/5-fluorouracil/folinic acid (FOLFIRI); or, first-line capecitabine/oxaliplatin (XELOX) followed by FOLFIRI[4]. The prognosis of patients with mCRC undergoing second-line treatment is poor and the expected median overall survival is approximately one year[5].

Aflibercept is a recombinant human fusion protein which blocks the vascular endothelial growth factor (VEGF) pathway by preferentially binding to VEGF-A, VEGF-B and placenta growth factor (PIGF). By blocking this pathway, aflibercept is believed to exert direct anti-cancer activity and to potentiate the anti-cancer activity of chemotherapy agents[5].

NICE has previously assessed and not recommended the use of aflibercept for the indication under consideration[6]. An updated All Wales Medicines Strategy Group (AWMSG) application has been made for aflibercept, which includes a Wales Patient Access Scheme (WPAS) and additional information specific to NHS Wales[1].

2.2 Comparators

The comparator included in the company submission was the chemotherapy regimen irinotecan/5-fluorouracil/folinic acid (FOLFIRI)[1].

2.3 Guidance and related advice

- NICE. Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy. Technical Appraisal (TA) 307 (2014)[6].
- NICE. Colorectal cancer: the diagnosis and management of colorectal cancer. Clinical Guideline (CG) 131 (2011)[4].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of a phase III clinical study (VELOUR) to evaluate the efficacy and safety of aflibercept plus FOLFIRI versus placebo plus FOLFIRI in patients with mCRC, following failure of an oxaliplatin-based regimen[1]. The submission also includes combined interim results from two ongoing non-randomised studies (collectively referred to as ASQoP) to evaluate safety and health-related quality of life (HRQoL). A systematic literature review was undertaken to identify studies evaluating second-line treatment of mCRC: only the VELOUR study was identified[1].

3.1 VELOUR study

VELOUR was a multinational, multicentre, phase III randomised, double-blind, placebo-controlled study conducted in 1,226 adult patients with histologically or cytologically proven mCRC, following disease progression while on or after completion of treatment with a single oxaliplatin-based regimen (i.e. second-line treatment)[1,5,7]. Patients were assigned 1:1 to receive 4 mg/kg aflibercept (n = 612) or placebo (n = 614) intravenously (IV), over one hour on day one every two weeks, followed immediately by the FOLFIRI regimen. Treatment was administered until occurrence of disease progression or unacceptable toxicity[1,5,7].

The primary endpoint was median overall survival (OS) defined as the time from randomisation to death from any cause[1,5,7]. Median follow up time for the primary analysis was 22.28 months. There was a statistically significant improvement in OS in the aflibercept plus FOLFIRI group compared with the placebo plus FOLFIRI group of 1.44 months, representing an 18.3% relative reduction in risk of death. Two year survival rates were 28.0% in the aflibercept group and 18.7% in the placebo group. The OS effect was supported by secondary endpoints: progression-free survival (PFS) and objective response rate (ORR). The applicant company also presented supportive pre-specified subgroup analyses; however, the submission focuses on the pre-specified subgroup of patients with the presence of liver metastasis only, and a post- hoc analysis excluding patients who had relapsed within six months of completion of oxaliplatin-based therapy. See Table 1 for summary of results.

Table 1. Summary of endpoints from the VELOUR study.[1,5,7]

Endpoint	Aflibercept plus FOLFIRI (n = 612)	Placebo plus FOLFIRI (n = 614)	Treatment difference	CI (p-value)
Primary endpoint				
Median OS	13.50 months	12.06 months	1.44 months HR: 0.817	95.34% CI: 0.713–0.937 (p = 0.0032)
Secondary endpoints				
Median PFS (independent assessment)	6.90 months	4.67 months	2.23 months HR: 0.758	95% CI: 0.661–0.869 (p = 0.00007)
ORR by RECIST (number of patients [%])	105 (19.8%)	59 (11.1%)	46 (NR) NR	NR (p = 0.0001)
Subgroup analysis: patients with liver metastasis only (pre-specified)				
Number of patients	153	146	–	–
Median OS	*	*	* HR: 0.649	95.34% CI: 0.492–0.855 (p = *)
Median PFS	*	*	*	*
Subgroup analysis: excluding patients who had relapsed within six months of completion of oxaliplatin-based adjuvant therapy (post-hoc)				
Number of patients	552	550	–	–
Median OS	13.8 months	11.9 months	1.9 months HR: 0.78	95% CI: 0.68–0.90 (p = 0.1265)
Median PFS	*	*	*	*

*Commercial in confidence figures removed.
CI: confidence interval; HR: hazard ratio; NR: not reported; ORR: objective response rate (defined as the percentage of patients achieving a confirmed complete or partial response according to RECIST); OS: overall survival; PFS: progression-free survival (defined as the time interval from the date of randomisation to the date of first observation of disease progression or death due to any cause); RECIST: Response Evaluation Criteria in Solid Tumours.

3.2 The global aflibercept safety and quality-of-life program (ASQoP) study

ASQoP is an on-going, phase IIIb/4, international, multicentre, single-arm, open-label study which is investigating the safety (primary objective) and HRQoL (secondary objective) of aflibercept in patients with mCRC previously treated with an oxaliplatin-based regimen[1]. [Commercial in confidence data removed].

3.3 Comparative safety

Evidence of comparative safety in the company submission comes from the VELOUR study[1]. A meta-analysis of pooled data from three phase III studies of aflibercept (VELOUR, VITAL [non-small cell lung cancer] and VANILLA [metastatic pancreatic cancer]) is also presented[8]. In addition, interim results from the ASQoP study is included in the company submission[1].

In the VELOUR study, treatment-emergent adverse events (AEs) were reported in 99.2% and 97.9% of the aflibercept arm and placebo arm patients, respectively. Permanent discontinuation of treatment occurred in 26.8% of patients in the aflibercept arm compared to 12.1% of patients in the placebo arm[1,5]. Severe AEs with a frequency ≥ 2% higher in the aflibercept group included diarrhoea, hypertension, asthenic conditions, stomatitis and ulceration, and dehydration[5]. Serious AEs (SAEs) were reported in 48.1% and 32.7% of patients in the aflibercept and placebo groups, respectively. The most common SAEs were gastrointestinal disorders (20% vs. 11%) followed by infection and infestations (11.3% vs. 6.3%)[5].

Meta-analysis of selected AEs using pooled data from the three phase III studies supported the overall findings of the VELOUR study. The risk of grade 3 or 4 anti-VEGF class AEs was increased when adding aflibercept to concurrent therapies. The increased risk was statistically significant only for hypertension.

Interim safety results from the ASQoP study are also presented[1]. [Commercial in confidence data removed].

3.4 AWTTC critique

- Aflibercept is licensed as second-line treatment for mCRC in combination with FOLFIRI chemotherapy. Current second-line treatment options within NHS Wales are largely limited to FOLFIRI treatment alone. Other biologic treatments (bevacizumab[9], cetuximab[10] and panitumumab[11]) are also licensed for use in mCRC although these are not currently recommended as treatment options[12]; however, they are available via national commissioning routes in England[13]. Aflibercept is also available via a commissioning route in England[13] and via Health Technology Assessment in Scotland[14]. The applicant company therefore highlight the current unmet need in Wales. This is also supported by clinical expert opinion sought by AWTTC.
- At the time of licensing the Committee for Medicinal Products for Human Use (CHMP) noted in the second-line setting of mCRC a median OS of approximately one year is currently expected. CHMP concluded that the superiority of aflibercept in combination with FOLFIRI over placebo combined with FOLFIRI in terms of OS was shown convincingly in the pivotal study although the effect was small (median OS was 1.44 months). At 30 months, a sustained positive effect of aflibercept was still present with a survival probability twice as high as in the placebo arm (22.3% versus 12%)[5].
- In the pivotal study, efficacy analyses were conducted in the randomised population and time-to-event parameters were estimated using Kaplan-Meier analysis. The applicant company highlight the Kaplan-Meier curves for OS started to separate early and continued to separate beyond the median, suggesting there were patients who experienced a sustained benefit following treatment with aflibercept plus FOLFIRI. The company conclude that the median estimate does not provide full representation of the survival benefit and therefore, present a post-hoc analysis of the mean OS. Using the log-logistic function to the observed data and extrapolating the survival curves over 15 years, aflibercept provided a mean OS of 4.7 months (95% confidence interval [CI]: 2.1 to 6.1) in favour of aflibercept plus FOLFIRI versus placebo plus FOLFIRI (22.8 months and 18.1 months, respectively)[1].
- Results are presented for the whole population of the VELOUR study, however the company also highlight two subgroups; patients with liver metastasis only (pre-specified) and excluding patients who had relapsed within six months of completion of oxaliplatin-based adjuvant therapy (post-hoc). However, the study was not powered to demonstrate superiority of aflibercept over placebo in any particular pre-specified subgroup[5]. Also, it is unclear whether these subgroups of patients would be identified and treated differently in clinical practice in Wales.
- A further pre-specified subgroup has been highlighted of interest by clinical experts in Wales; patients who had not received prior treatment with bevacizumab. A numerically greater treatment effect on OS with the aflibercept plus FOLFIRI regimen was reported in patients with no prior bevacizumab as compared to patients with prior bevacizumab exposure[2]. Bevacizumab is not given routinely in Wales, thus the Welsh cohort of patients are likely to gain this additional benefit.

- CHMP noted that aflibercept is associated with anti-VEGF class side effects and adding aflibercept to FOLFIRI increased AEs typically associated with FOLFIRI[5]. The safety analysis from the meta-analysis of pooled data from three phase III clinical studies led CHMP to consider the following AEs to be of major clinical importance due to increased risk: hypertension, haemorrhage, gastrointestinal and non-gastrointestinal fistula. CHMP concluded that despite significant toxicity of aflibercept in combination with FOLFIRI, there was still a small but clinically significant survival advantage and thus, the benefits associated with aflibercept outweigh the risks[5].
- The company submission also includes non-trial patient outcome data from an on-going study (USAP study) (conference poster) being conducted at Velindre Cancer Centre in South Wales. Between July 2012 and March 2013, 20 patients received aflibercept, as an unlicensed therapy, who had failed first-line oxaliplatin-based chemotherapy and were about to start second-line irinotecan-based chemotherapy with FOLFIRI. The submission highlights the clinical team conclusion that aflibercept in combination with FOLFIRI, has a manageable side effect profile outside of clinical studies and that it appears to add a survival benefit in patients with mCRC with an acceptable toxicity profile[1,15].
- CHMP highlighted that no validated predictive serum or plasma biomarkers have been identified that correlate with treatment outcomes to aflibercept, however the applicant company is to retrospectively analyse plasma and tissue samples as part of post-authorisation measures[5].

4.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company has submitted a cost-utility analysis of aflibercept in combination with FOLFIRI chemotherapy compared to FOLFIRI alone in adult patients with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen (i.e. second-line treatment)[1]. The primary clinical data used in the economic model was from the VELOUR study. In addition, an economic assessment was performed for two subgroups: patients with liver metastasis (approximately 25% of the VELOUR study patients); and a subgroup excluding patients who had progressed within six months of oxaliplatin-based adjuvant therapy (approximately 10% of VELOUR patients excluded). A Markov model was used with health states consisting of stable, non-progressive disease (subdivided into: on second line, and discontinued second-line treatment due to AEs and other reasons, but not progressed), progressive disease and dead. A model cycle length of two weeks was assumed with a 15-year time horizon. Parametric functions were fitted based on best statistical and visual fit to the observed clinical data in order to extrapolate OS, PFS and time to treatment discontinuation pre-progression and up to disease progression[1].

Utility estimates for the model health states were based on EQ-5D data from the ASQoP study (see Section 3.2). [Commercial in confidence data removed]. Disutilities for grade 3 or 4 AEs with > 5% incidence, and six rarer but clinically important AEs (based on clinical expert opinion) were based on published estimates[1].

The cost per two week cycle for aflibercept at list price is £295.65 and £591.30 for 100 mg and 200 mg vials respectively. [Commercial in confidence data removed]. Estimates of duration of treatment, number of administrations, dose reductions and delays (dose intensity) were as observed in the VELOUR study. The base case assumption was of no drug wastage in administration of vials, and a 10% additional

administration cost was included for aflibercept plus FOLFIRI based on clinical expert opinion that additional resource would be required over that needed for FOLFIRI administration alone. Hospital resource use associated with mCRC disease management was estimated from a retrospective UK observational resource use study in four UK treatment centres (one centre in Wales). [Commercial in confidence data removed][16]. Community and social care costs were also included based on a questionnaire survey with six UK clinical oncologists, with estimates covering resources used in medicine regimen switch, GP use, AE management, residential, community health care, day care, hospice use and other community based services. The costs of subsequent active therapy and best supportive care after aflibercept plus FOLFIRI or FOLFIRI alone (i.e. after second-line discontinuation and after disease progression) was based on treatment received in the VELOUR study[1].

For the sub-groups, the same approach was adopted for extrapolating OS, PFS and estimating treatment discontinuation as in the main analysis, although Kaplan-Meier data was used for PFS as none of the parametric functions tested provided a good fit to the observed data. Specific subgroup data from the VELOUR study for duration of treatment, number of administrations, dose intensity, body weight/BSA and AE probabilities were applied[1].

4.1.2 Results

The estimated incremental cost per Quality Adjusted Life Year (QALY) gained for the base case comparison of aflibercept plus FOLFIRI versus FOLFIRI alone, taking into account the WPAS, is £38,173. [Commercial in confidence data removed]. The main driver of the results is the additional medicine acquisition costs of aflibercept, but also additional administration costs, and disease management costs and QALYs associated with longer time for the aflibercept patients spent in both the pre- and post-progression health states, although approximately 60% of the QALY gain was associated with longer time spent in post progression. AE costs were also higher for the aflibercept plus FOLFIRI group[1].

Table 2. Base case analysis results with WPAS[†1].

	Aflibercept plus FOLFIRI	Placebo plus FOLFIRI	Increment
Medicine costs	*	*	*
Other costs[§]	*	*	*
Total costs	*	*	*
Life years gained	*	*	*
QALYs gained	*	*	*
ICER (deterministic)			£38,173

[*]Commercial in confidence figures removed.
[†]Costs and benefits discounted at 3.5% per annum.
[§]These cover aflibercept plus FOLFIRI and FOLFIRI medicine administration costs, pre-progression subsequent medicine and administration, disease management, adverse event (AE) and regimen switch costs, and post-progression medicine and administration costs and disease management costs. A cost for end-of-life care was not included as it was assumed this would be the same for both treatment arms.
ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality-Adjusted Life Year.

For the subgroups analysis, the company estimated an Incremental Cost-Effectiveness Ratio (ICER) of £29,994 per QALY gained for patients with liver metastasis, and

£34,151 per QALY gained excluding patients who had progressed within six months of oxaliplatin-based adjuvant therapy (Table 3)[1].

In deterministic sensitivity analysis the ICER was most sensitive to varying utility estimated for progressive disease by its 95% confidence intervals (CIs). The results were not sensitive to varying the utility assumed for end-of-life between 0.2 to 0.4, or varying patient weight or the 95% CIs for OS.

In scenario analysis, the results were not particularly sensitive to increasing the time horizon to 25 years, or reducing it to ten years (Table 3). However, a time horizon of five years increased the ICER to £50,598/QALY. [Commercial in confidence data removed]. As the OS data from the VELOUR study was relatively mature, a pessimistic scenario in which no extrapolation is performed (i.e. the Kaplan-Meier data is used for OS) resulted in an ICER of £63,263 per QALY gained, [Commercial in confidence data removed] (Table 3).

Probabilistic sensitivity analysis based on 5,000 simulations indicated an 11% probability of aflibercept plus FOLFIRI being cost-effective at a threshold of £30,000/QALY gained, and 90.1% at a threshold of £50,000/QALY gained[1].

Table 3: Subgroup and selected scenario/sensitivity analyses[1].

Subgroup or sensitivity analysis	Incremental cost	Incremental LYG	Incremental QALY	ICER	Plausibility
Subgroup of patients with liver metastasis	*	*	*	£29,994	The NICE Appraisal Committee for the TA of aflibercept plus FOLFIRI expressed concerns over the lack of evidence of additional benefit in this sub-group, in terms of facilitating the use of curative resection of liver metastasis. An additional clinical benefit is uncertain due to the data coming from a subgroup in the VELOUR study not powered to show differences in PFS or survival outcomes.
Subgroup of patients excluding those relapsing within six months of prior oxaliplatin-based adjuvant therapy	*	*	*	£34,151	This subgroup represented 90% of the patients in the VELOUR study, hence is limited in using it to identify patients who may not obtain relatively less benefit from aflibercept plus FOLFIRI.
Utility associated with progressive disease – upper bound 95% CI *	*	*	*	£35.357	The majority of the QALY gain is obtained from time in the post-progression state, hence the ICER range here plausibly reflects the level of uncertainty in utility associated with progressive disease.
Varying utility associated with progressive disease by lower bound 95% CI *	*	*	*	£41,261	
Weibull function fitted to estimate OS	*	*	*	£51,385	There is uncertainty over the base case ICER due to limitations in the extrapolation of survival outcomes associated with using a truncated log-logistic function in the base case in that OS estimate is much greater than the trial based estimate. The Weibull curve produces a lower extrapolated OS estimate and so provides a plausible upper ICER estimate. Note survival benefit is three months undiscounted, hence borderline for end-of-life criteria.
Applying Kaplan-Meier to OS	*	*	*	*	This scenario enables a relatively robust upper 'pessimistic' estimate of the ICER as based on observed data only for OS. Note survival benefit is < three months undiscounted, hence not within usual end-of-life criteria.
Time horizon 25 years	*	*	*	£36,413	Unlikely to be a more plausible time horizon than the 15 years chosen in the base case.
Time horizon ten years	*	*	*	£40,817	Shorter time horizons may be more reflective of the extent to which it is plausible to extrapolate beyond the study data. Ten years maybe more plausible for the base case, whereas five years maybe a little pessimistic.
Time horizon five years	*	*	*	£50,598	

*Commercial in confidence figures removed.
CI: confidence interval; ICER: Incremental Cost-Effectiveness Ratio; LYG: life years gained; OS: overall survival; PFS: progression-free survival; QALY: Quality-Adjusted Life Year; TA: technology appraisal.

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. The base case ICER is over £30,000 per QALY gained, but the company have argued that aflibercept plus FOLFIRI meets AWMSG specified end-of-life criteria (see section 6.5). An important uncertainty in the economic evaluation is the estimated survival benefit associated with aflibercept plus FOLFIRI compared to FOLFIRI alone. The median survival improvement from the VELOUR study was 1.44 months, whereas in the economic analysis the mean (undiscounted) survival benefit was estimated at 4.7 months based on extrapolation using a log-logistic parametric function. In addition to FOLFIRI, NICE guidance also specifies irinotecan monotherapy as a second-line option, but was argued by the company not to be a relevant comparator on the grounds it tends to be reserved for patients who are not able to tolerate further fluorouracil-based therapy, and use in practice is low.

Strengths of the economic evidence include:

- An appropriate simple model structure which was clearly specified.
- Clinical study data versus an appropriate comparator from a large clinical study with a relevant patient population and relatively mature PFS and OS data for the economic evaluation. Irinotecan is a potential comparator, but not an important one due to low use relative to FOLFIRI in the target patient population for aflibercept plus FOLFIRI.
- The availability of EQ-5D data from a phase IIIb/4 study in similar patients as the VELOUR study, and resource use data from a real world study, which have enabled relatively reliable estimates of pre- and post-progression utility and disease management resource use respectively (although patient numbers are relatively limited in the latter study).

Key limitations of the economic evidence include:

- Uncertainty over the extrapolation of life years and hence QALY gains associated with aflibercept plus FOLFIRI. A log-logistic function was fitted in the base case and due to a long tail was truncated at 15 years, to produce a mean (undiscounted) survival benefit of 4.7 months. This is in contrast to an estimated mean survival benefit without OS extrapolation of 2.2 months, or 3.0 months undiscounted when the Weibull function was used. The log-logistic function may therefore overestimate the survival benefit and the plausible ICER range maybe better approximated by the Weibull function (to provide an upper ICER of £51,000/QALY), and that estimated by adopting a shorter, less uncertain time horizon to limit the extent of extrapolation with the log-logistic function (£40,100/QALY with ten years).
- The estimates of resource use and costs associated with community and personal social care are uncertain as are based only on expert opinion, but also use median estimates rather than mean estimates of resource use. The use of medians may have resulted in underestimated costs for this component of care in pre- and post-progression health states, which is favourable for the cost-effectiveness of aflibercept plus FOLFIRI as patients spend longer time in these states compared to FOLFIRI patients.
- The subgroups considered may either lack clinical relevance (in the case of the subgroup excluding those who had progressed within six months of oxaliplatin-based adjuvant therapy), or have limitations in the evidence to support an additional benefit (as is the case for the subgroup with liver metastasis). Hence, the improved cost-effectiveness for these subgroups relative to the whole patient population is uncertain.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) did not identify any published evidence specifically on the cost-effectiveness of aflibercept plus FOLFIRI within its current licensed indication for patients with mCRC. NICE and Scottish Medicines Consortium (SMC) guidance has been issued which covers the cost-effectiveness evidence for aflibercept plus FOLFIRI based on the same economic model submitted for these TAs[6,14]. The NICE TA guidance in particular expressed the greatest concerns over the robustness of survival extrapolation used in the economic analysis as it was based on a parametric function with a long tail, and concerns that the utility estimated for progressive disease (0.708) was too high. The ICER for the preferred base case assumptions of the NICE Appraisal Committee based on a utility of 0.6 for progressive disease and higher patient age than in the company's model (65 years instead of 60 years), resulted in an ICER of £51,000/QALY gained which would be higher if an extrapolation function with a less heavy tail had been used. The ICER estimated in the SMC submission was £34,623/QALY gained with a PAS applied. The ICER was noted as being sensitive to the overall survival function used (a Weibull function increased the ICER to £47,000/QALY). The model structure and survival modelling submitted to NICE and SMC were broadly the same as in the AWMSG submission, although new EQ-5D data was used for health state utility estimates[6,14].

5.0 ASSESSMENT OF THE EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Estimates of the numbers of patients with CRC were obtained from the latest National Cancer Registry for Wales[17] with proportions estimated to be diagnosed metastatic or to develop metastasis in each year obtained from a European clinical guidelines publication (ESMO)[18], resulting in an estimated 1,528 mCRC patients in Wales. [Commercial in confidence data removed]. Of the 382 patients estimated to be receiving second-line therapy, 64% (244 patients) were estimated to have received first-line oxaliplatin-based regimen hence eligible for aflibercept plus FOLFIRI. The numbers of eligible patients is assumed to be stable over a five year time period, supported by age-standardised incidence data for bowel cancer from Cancer Research UK showing no meaningful change over the last ten years. The expected number of treated patients are based on aflibercept plus FOLFIRI uptake rates of 15% in year one rising each year to 59% in year five (Table 4).

5.1.2 Results

[Commercial in confidence data removed]. Without WPAS the net budget impact is estimated to be £299,000 in year one rising to £1,720,000 in year five (Table 4).

Table 4. Company-reported base case budget impact of aflibercept plus FOLFIRI in Wales.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication[s] covered in this submission)	244	244	244	244	244
Uptake in incident patient population (%)	15%	25%	40%	50%	59%
Treated patients	37	61	98	122	144
Net costs					
Net costs (medicine costs) without WPAS	£298,844	£498,074	£796,918	£996,148	£1,172,466
Net costs (medicine costs) with WPAS	*	*	*	*	*
Administration and monitoring	N/A	N/A	N/A	N/A	N/A
*Commercial in confidence figures removed. N/A: not available; WPAS: Wales Patient Access Scheme.					

5.1.3 AWTTC critique

- The published sources used for estimating number of patients with mCRC seem reasonable, although the estimates of patients receiving first- or second-line therapy who have received a first-line oxaliplatin-based regimen and hence are eligible for aflibercept are based only on market research and hence are uncertain.
- The derivation of the uptake rates estimated have not been explained hence are also highly uncertain.
- No sensitivity analysis has been performed around the uncertain variables; e.g. percentage receiving second-line therapy, and proportion of patients who have received first-line oxaliplatin-based therapy.
- The company have not included the impact of potential additional administration and other resource costs associated with aflibercept in combination with FOLFIRI.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

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

The company do not anticipate that aflibercept (Zaltrap®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The ASQoP study will provide relevant evidence within the next 12 months (see section 3.2 for interim results).

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: 3 and 12 September 2014

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

Consideration is required as to whether aflibercept in the given patient population meets the end-of-life criteria set by the AWMSG Policy on appraising life-extending, end-of-life medicines[20].

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 three 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 study, or projected life years gained) should be robust and shown (or reasonably inferred) from either PFS or OS.
- AWMSG/The New Medicines Group (NMG) will consider the cumulative population of each licensed indication of the medicine to be small.

The applicant company's base case ICER for aflibercept plus FOLFIRI exceeds £30,000 per QALY when compared with FOLFIRI alone. The company suggest that aflibercept in combination with FOLFIRI should be considered within the context of AWMSG policy for appraising life-extending, end-of-life medicines.

Median OS associated with second-line treatment of patients with mCRC after first-line treatment with an oxaliplatin-based regimen was estimated to be 12.1 months for the control arm (placebo plus FOLFIRI) in the VELOUR study[7]. The modelled mean OS in the FOLFIRI group of the economic model is 18.1 months.

Mean survival was estimated to be increased for aflibercept plus FOLFIRI patients compared to FOLFIRI alone by an average of 4.7 months based on fitting a truncated log-logistic and parametric function to the observed OS data in the VELOUR study (i.e. this function was selected based on providing the best statistical and visual fit). However, based on the observed Kaplan-Meier data in the VELOUR study the improvement in estimated median OS was an improvement of 1.44 months for aflibercept plus FOLFIRI over FOLFIRI alone[7]. The company comments that the Kaplan-Meier curves diverge early and continue to diverge beyond the median and therefore suggest that this underestimates the actual OS benefit of aflibercept. The applicant company has argued that mean OS is more appropriate to consider in cost-effectiveness modelling[21], and contends that based on projected mean OS estimated, the second-line use of aflibercept with FOLFIRI would meet AWMSG end-of-life survival benefit criteria. There are some concerns over the robustness of the log-logistic function estimates of mean survival. However, applying a range of alternative viable functions resulted in estimates of mean survival improvement ranging from 3.0 months based on fitting a Weibull function, to 4.7 months with the 'truncated' log-logistic function used in the base case of the economic analysis or 5.2 months with a log-normal function. Applying only the Kaplan-Meier data to estimate OS produces a mean survival of 2.2 months, so below the three months criteria. Overall, based on the estimates generated it could be considered probable that the survival benefit of the intention to treat (ITT) population of the VELOUR study reaches at least three months, although whether it is any greater than this is uncertain.

NICE considers that ≤ 7,000 patients in England would be considered to meet the definition of small under its end-of-life policy. Based on Office for National Statistics

mid-2012 population estimates (53.5 million in England; 3.1 million in Wales)[22], thus a small cumulative population would equate to 406 patients in Wales. The company has estimated an eligible patient population in Wales for second-line aflibercept plus FOLFIRI of 244 patients. However, a lack of sensitivity analysis for key parameters in the budget impact estimate provided means it is unclear whether patient numbers could potentially exceed 406, although it is unlikely that significantly higher patient numbers are eligible.

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