Re-Submission:

aflibercept 25mg/mL concentrate for solution for infusion (Zaltrap®)

Sanofi

07 February 2014

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 Scotland. The advice is summarised as follows:

**ADVICE:** following a resubmission

aflibercept (Zaltrap®) is accepted for use within NHS Scotland.

**Indication under review:** in combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy, aflibercept is indicated in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

In one randomised, double-blind, phase III study, aflibercept plus FOLFIRI chemotherapy regimen resulted in statistically significant longer overall survival compared with placebo plus FOLFIRI chemotherapy regimen. However the effect was of relatively modest clinical benefit.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of aflibercept. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
### Indication

In combination with irinotecan/5-fluorouracil/folinic acid (FOLFIRI) chemotherapy, aflibercept is indicated in adults with metastatic colorectal cancer (mCRC) that is resistant to or has progressed after an oxaliplatin-containing regimen.

### Dosing Information

Aflibercept should be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Aflibercept 4mg/kg of body weight administered as a intravenous (iv) infusion over 1 hour followed by the FOLFIRI regimen. This is considered as one treatment cycle and the treatment cycle is repeated every 2 weeks. Aflibercept treatment should be continued until disease progression or unacceptable toxicity occurs.

[FOLFIRI regimen; irinotecan 180mg/m² iv infusion over 90 minutes and folinic acid (dl racemic) 400mg/m² iv infusion over 2 hours at the same time on day 1 using a Y-line, followed by 5-fluorouracil (5-FU) 400 mg/m² iv bolus, followed by 5-FU 2400 mg/m² continuous iv infusion over 46 hours].

### Product availability date

March 2013

### Summary of evidence on comparative efficacy

Aflibercept is a recombinant human fusion protein which blocks the vascular endothelial growth factor (VEGF) pathway affecting VEGF-A, VEGF-B and placental growth factor (PIGF). It is licensed for use in combination with the FOLFIRI chemotherapy regimen in patients with metastatic colorectal cancer (mCRC) who have progressed on, or are resistant to, an oxaliplatin-containing regimen and, therefore, the only relevant comparator is the FOLFIRI chemotherapy regimen.

One randomised, placebo-controlled, phase III study (VELOUR) has been conducted in 1,226 adult patients with histologically or cytologically proven mCRC previously treated with a single oxaliplatin-containing regimen. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. Patients were not selected for the timing of their progression; patients who had relapsed within 6 months of completion of oxaliplatin-containing regimen were eligible. Prior treatment with bevacizumab was permitted.

Patients were randomised equally to receive aflibercept 4mg/kg administered as an intravenous (iv) infusion over one hour immediately followed by FOLFIRI (n=612), or to receive placebo plus FOLFIRI (n=614). The treatment regimens were repeated every two weeks until occurrence of disease progression or unacceptable toxicity according to physician judgement. Randomisation was stratified according to prior therapy with bevacizumab (yes or no) and ECOG PS (0, 1 or 2).

The primary endpoint was overall survival, defined as the time interval from randomisation to death from any cause. The median duration of follow-up at the cut-off date for survival analysis was 22.3 months and there were 403 events (66%) in the aflibercept group versus 460 events (75%) in the placebo group. Median overall survival was statistically significantly longer for aflibercept (13.50
months) than placebo (12.06 months): stratified hazard ratio 0.82 (95.34% confidence interval [CI] 0.71 to 0.94), p=0.0032. Survival rates at 2 years were 28% versus 19% respectively. In a pre-specified subgroup analysis (based on prior treatment with bevacizumab), median overall survival was significantly longer with aflibercept versus placebo in the subgroup who did not receive prior bevacizumab (n=853; hazard ratio 0.79 [95.34% CI: 0.67 to 0.93]). Other subgroup analyses for overall survival (and progression free survival [PFS]) according to age (<65 years; ≥65 years), gender, presence of liver metastasis only, history of prior hypertension, and number of organs involved, showed a treatment effect favouring aflibercept over placebo.  

Secondary endpoints included PFS and response rate. PFS was assessed by an independent review committee and was defined as the time interval from the date of randomisation to the date of progression, or death from any cause if it occurred before tumor progression was documented. Median PFS was statistically significantly longer for aflibercept (6.90 months) than placebo (4.67 months): stratified hazard ratio 0.76 (95% CI 0.66 to 0.87), p<0.0001. Response rate included complete and partial responses and was assessed by the independent review committee using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 in patients who had measurable disease at baseline. The response rate was 20% (105/531) in the aflibercept group and 11% (59/530) in the placebo group, p<0.001. There were no complete responses in the aflibercept group versus two in the placebo group and the remainder were partial responses. No quality of life data were collected.

A post-hoc extended analysis of mean overall survival for the VELOUR study has been published. Mean overall survival was estimated by fitting a number of parametric functions to the study data and extrapolating to provide complete curves. The log-logistic function appeared to provide the best overall fit (based on Akaike information criterion and Bayesian information criterion). The estimated mean overall survival over an applied cut-off of 15 years was 22.8 months for the aflibercept group and 18.1 months for the placebo group; difference 4.7 months (95% CI 2.1 to 6.1). At an applied cut-off of 5 years the difference in mean overall survival was 3.0 months (95% CI 1.2 to 4.9).

Two on-going, open-label, single-arm studies (ASQoP and AFEQT) aim to assess the safety and quality of life of aflibercept (plus FOLFIRI) in patients with mCRC previously treated with an oxaliplatin-based regimen. The inclusion and exclusion criteria were similar to the VELOUR study, with the exception that patients with an ECOG PS ≥2 were excluded. The EQ-5D instrument was used as the utility measure and the five-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) three-level system was converted into a single index utility score (minimum value of -0.594 and a maximum value of 1.0). Data from 67 patients were included in an interim pooled analysis. At baseline the mean EQ-5D single-index utility score was 0.77 and at cycle three (n=63 evaluable patients) it was 0.78 (mean change +0.01 [95% CI -0.04 to 0.08]). At cycle five (n=30 evaluable patients) the EQ-5D single-index utility score was 0.79 (mean change -0.02 [95% CI -0.12 to 0.07]). Similar results were observed for the EQ-5D visual analogue scale (VAS) scores.

### Summary of evidence on comparative safety

Treatment emergent adverse events were reported in 99% of aflibercept treated patients and 98% of placebo treated patients, and resulted in permanent study discontinuation in 27% (164/611) of aflibercept patients and 12% (73/605) of placebo patients. Grade 3/4 treatment-related adverse events were reported in 74% (451/611) versus 47% (284/605) of patients respectively. The incidences of the following grade 3/4 adverse events were higher in the aflibercept arm (and reported in >2% of patients): hypertension (19% versus 1.5%), diarrhoea (19% versus 7.8%), haemorrhage (2.9% versus 1.7%), stomatitis and ulceration (14% versus 5.0%), asthenic conditions (17% versus
11%); gastro-intestinal and abdominal pain (5.4% versus 3.3%), dehydration (4.3% versus 1.3%), palmar-plantar erythrodysesthesia syndrome (2.8% versus 0.5%) and proteinuria (7.9% versus 1.2%).

Serious adverse events occurred in 48% (294/611) of aflibercept patients and 33% (198/605) of placebo treated patients. The most common serious adverse events were gastrointestinal disorders (20% versus 11%), infection and infestations (11% versus 6.3%), blood and lymphatic system disorders (6.5% versus 2.5%), metabolism and nutrition disorders (4.9% versus 1.8%) and respiratory, thoracic and mediastinal disorders (5.9% versus 3.0%). Adverse events were the cause of death (within 30 days from last dose) in 14 (2.3%) aflibercept treated patients versus four (0.7%) of placebo treated patients.

### Summary of clinical effectiveness issues

Scottish Intercollegiate Guideline Network (SIGN) guidance recommends that mCRC is treated first-line with combination chemotherapy including 5-FU/folinic acid/oxaliplatin (FOLFOX), or capecitabine plus oxaliplatin, or 5-FU/folinic acid/irinotecan (FOLFIRI). Choice of second-line treatment depends on patient fitness, co-morbidity and previous chemotherapy exposure. Aflibercept is licensed for use in combination with FOLFIRI for mCRC resistant to or which has progressed after an oxaliplatin-containing regimen.

The pivotal study demonstrated statistically significant longer median overall survival in patients with mCRC treated with aflibercept (plus FOLFIRI) compared to placebo (plus FOLFIRI). Results of the secondary endpoints were supportive of the primary endpoint. The chemotherapy regimen, FOLFIRI, is an appropriate comparator and the study inclusion criteria matched the patient population eligible for aflibercept in terms of the licensed indication. Median overall survival was significantly longer in the sub-group of patients (approximately 70%) who had not received prior treatment with bevacizumab. This subgroup is more likely to represent patients in clinical practice in Scotland where the National Institute for Health and Care Excellence (NICE) multiple technology appraisal (MTA) 118 is valid, and does not recommend bevacizumab.

There are some limitations with the VELOUR study results and design. While median overall survival was significantly longer for aflibercept treated patients, the additional median survival of 1.44 months is small. Clinical experts consulted by SMC considered that aflibercept is a therapeutic advancement but it is of modest clinical benefit. The submitting company argued that median overall survival does not provide a full picture of the survival benefit of aflibercept and that mean overall survival provides a more meaningful estimate. Using the log-logistic function over 15 years, aflibercept provided an additional mean survival of 4.7 months. However the statistician consulted by SMC advised that, as an estimate of average benefit, the median overall survival is of more relevance. The median overall survival is the accepted measure in considering clinical effectiveness but for health economic analyses the mean is used. It captures the benefits over a longer period of time and allows these to be included in the cost effectiveness estimate.

Whilst quality of life was not assessed in the study, an interim pooled analysis of two on-going, single-arm, open-label studies indicates that the mean EQ-5D single-index utility and VAS scores remained stable at cycle 3 and 5. However, in these single-arm studies a higher proportion of patients had an ECOG PS of 0 (73%) than in the VELOUR study (57%).

In the VELOUR study, patients were treated until disease progression or unacceptable toxicity and the median overall number of cycles in the aflibercept and placebo groups was nine and eight respectively. Clinical experts consulted by SMC reported their current practice is for FOLFIRI to be
administered for a fixed number of cycles (between 9 to 12 cycles). Therefore, there may some uncertainties in terms of the generalisability of the study results to clinical practice in NHS Scotland.

The addition of aflibercept to FOLFIRI was associated with significant toxicity that was not always manageable clinically, and for some patients resulted in termination of FOLFIRI chemotherapy as well. A higher proportion of patients discontinued treatment in the aflibercept group (27%) than the placebo group (12%). The European Medicines Agency (EMA) noted that aflibercept is associated with anti-VEGF class adverse events. The risk (relative to placebo) of these events has been estimated from a meta-analysis which included data from three phase III studies in various cancers (including the study described previously). The aflibercept-associated anti-VEGF class adverse events considered to be of major clinical importance because of increased risk were hypertension, haemorrhage and gastrointestinal and non-gastro-intestinal fistulae.3

The EMA noted that that the company plans to analyse plasma and tissue samples from three studies (including the pivotal study) retrospectively, with the primary aim being to determine prognostic or predictive biomarkers correlating with overall survival. It is hoped that this information, expected at the end of 2016, will help to define better the target population.3

The availability of aflibercept will require the addition of an iv infusion of one hour duration to the FOLFIRI chemotherapy regimen currently used. Clinical experts consulted by SMC considered that the introduction of aflibercept may impact on the patient in terms of length of clinic visit and for service delivery in terms of the requirement for the preparation and administration of an additional infusion.

### Summary of comparative health economic evidence

The company submitted a cost-utility analysis over a 15-year time horizon comparing aflibercept plus FOLFIRI to FOLFIRI alone in patients with mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen. A Markov model was used which consisted of three main health states: ‘stable, non-progressive disease’, ‘progressed disease’ or ‘dead’. The stable disease health state was separated into two sub states of ‘on second-line treatment’ and ‘discontinued second-line treatment’. The model structure and choice of comparator are appropriate.

The clinical data used in the model were taken from the pivotal study described above. Overall survival data were extrapolated using the log-logistic function, which was estimated to be the best fit to the study data based on goodness-of-fit statistics and visual inspection of the curves. The company noted that as the log-logistic function has a long tail the analysis was truncated at 15 years to avoid overestimating survival.

In this resubmission, quality of life data from 67 patients were included from an interim pooled analysis of the ongoing open-label single-arm ASQoP and AFEQT studies. Based on these studies a revised utility value for the stable disease state was calculated using a weighted average of cycles 3 and 5. The utility value for the stable disease state was estimated at 0.78. The value for progressed disease, was taken from the mCRC observational utility study which was the source of the utility data in the original submission. A utility decrement of 0.3 was included in the base case for the last 3 months of the progressed disease health state to reflect a sharp decline in end stage quality of life.

Disease management costs were applied to each health state in the model using the results of an observational study which included patients who received an irinotecan-based chemotherapy regimen, combined with the results of a survey of six clinicians. These costs included supportive medicines, physician and nurse visits, imaging, laboratory tests, hospitalisations, palliative care, and personal and social care. A 10% additional administration cost was included in the aflibercept arm in order to reflect
expert concerns expressed during the previous review relating to the additional staff time needed to administer aflibercept in practice.

A revised PAS was submitted by the company and accepted by the Patient Access Scheme Assessment Group (PASAG). With the PAS, the submitting company estimated a cost per QALY of £34,623 based on an incremental cost of £8,519 and a quality adjusted life year (QALY) gain of 0.2460. The decrease in the base case cost per QALY was largely due to the PAS increase.

For the subgroup of patients with liver metastases the cost per QALY was estimated at £27,424 based on an incremental cost of £10,164 and a QALY gain of 0.3706. For the subgroup excluding patients who had progressed within 6 months of adjuvant therapy the cost per QALY was estimated to be £30,983 based on an incremental cost of £8,285 and a QALY gain of 0.2674.

In addition to the relatively high base case cost per QALY, the following weaknesses were noted:

• With PAS scenario analysis results provided by the company indicate that the incremental cost-effectiveness ratio (ICER) is most sensitive to the overall survival function used in the analysis. Using the Weibull function increases the ICER to £47k per QALY.
• The results did not appear to be overly sensitive to changes in the utility values. When the progressive disease utility value was decreased, the ICER increased to around £39k per QALY. The utility value for stable disease used in the analysis had a minimal effect on the ICER. Using the mCRC observational utility study value instead of the ASQoP study value of 0.78 resulted in an ICER of £35k.
• The utility value for the stable disease state has increased from 0.75 to 0.78 in this resubmission based on the weighted average of cycles from the ASQoP and AFEQT studies. For clarification purposes the company was asked to provide additional information on the patients within these studies as it was not clear from the submission how the data from the studies were pooled. However, clarification on this issue was subsequently provided by the company.

SMC considered the likely range of cost-effectiveness ratios for aflibercept in this setting and the remaining uncertainties in the economic case. The committee considered the benefits of aflibercept in the context of the SMC decision modifiers and agreed that the criteria of a substantial improvement in quality of life in the patient population targeted in the submission was satisfied and there being a subgroup of patients who may derive specific or extra benefit were satisfied. Although there were some limitations in the economic analysis, the committee agreed that the relatively high cost per QALY was acceptable given the expected benefits of the treatment and in the context of the decision modifiers.

Other data were also assessed but remain commercially confidential.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

SIGN published guideline number 126; diagnosis and management of colorectal cancer in December 2011.7 For mCRC the following recommendations are included;

First-line:
• All patients with mCRC should be considered for chemotherapy.
• Combination treatment with 5-FU/leucovorin/oxaliplatin or capecitabine and oxaliplatin or 5-FU/leucovorin/irinotecan are the preferred options in patients with good performance status and organ function.

• The choice of first-line chemotherapy for patients with mCRC will depend on patient fitness, comorbidity, and overall aim of treatment.

Second-line:

• Second-line chemotherapy should be considered for patients with mCRC with good performance status and adequate organ function.

• Irinotecan should be used as second-line therapy following first line oxaliplatin (or vice versa).

• The choice of second-line chemotherapy for patients with mCRC will depend on patient fitness, comorbidity and previous chemotherapy exposure.

Biological therapy:

• Cetuximab should be considered in combination with 5-FU/leucovorin/oxaliplatin or 5-FU/leucovorin/irinotecan chemotherapy for patients with unresectable liver metastases if patients fulfil the SMC criteria. The use of cetuximab in combination with oxaliplatin and capecitabine cannot currently be recommended.

NICE published clinical guideline 131; colorectal cancer; the diagnosis and management of colorectal cancer in November 2011. For mCRC the following recommendations are included:

When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer consider one of the following sequences of chemotherapy unless they are contraindicated:

• FOLFOX (folinic acid plus 5-FU plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or

• FOLFOX as first-line treatment then FOLFIRI (folinic acid plus 5-FU plus irinotecan) as second-line treatment or

• XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus 5-FU plus irinotecan) as second-line treatment.

• Decide which combination and sequence of chemotherapy to use after full discussion of the side effects and the patients preferences.

NICE published MTA 242 (cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy) in January 2012. The following advice is included:

• Cetuximab monotherapy or combination chemotherapy is not recommended for the treatment of people with mCRC that has progressed after first-line chemotherapy.

• Bevacizumab in combination with non-oxaliplatin (fluoropyrimidine-based) chemotherapy is not recommended for the treatment of people with mCRC that has progressed after first-line chemotherapy.

• Panitumumab monotherapy is not recommended for the treatment of people with mCRC that has progressed after first-line chemotherapy.

• People currently receiving cetuximab monotherapy or combination chemotherapy, bevacizumab in combination with non-oxaliplatin chemotherapy, or panitumumab monotherapy for the treatment of mCRC that has progressed after first-line chemotherapy should have the option to continue treatment until they and their clinician consider it appropriate to stop.

NICE published MTA 118 (bevacizumab and cetuximab for the treatment of metastatic colorectal cancer) in January 2007. This has been partially updated by MTA 242. The following advice is still valid

• Bevacizumab in combination with 5-FU plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of mCRC.

• People currently receiving bevacizumab (or cetuximab) should have the option to continue therapy until they and their consultants consider it appropriate to stop.
Additional information: comparators

FOLFIRI chemotherapy regimen.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per cycle (£)</th>
<th>Cost per course (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept plus FOLFIRI</td>
<td>aflibercept 4mg/kg plus FOLFIRI</td>
<td>887</td>
<td>7,983</td>
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<tr>
<td></td>
<td></td>
<td>685</td>
<td>6,165</td>
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<tr>
<td></td>
<td>Total cost=1,572</td>
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<td>14,148</td>
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<tr>
<td>FOLFIRI</td>
<td>irinotecan 180mg/m² iv infusion folinic acid 400mg/m² iv infusion 5-fluorouracil (5-FU) 400mg/m² iv bolus, followed by 5-FU 2,400mg/m² continuous iv infusion over 46 hours</td>
<td>685</td>
<td>6,165</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from; BNF September 2013. Costs based on a body weight of 70kg, a body surface area of 1.8m² and a course is based on 9 cycles (median number of cycles in aflibercept group of pivotal study). Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 286 in all five years.

Without PAS: The gross impact on the medicines budget was estimated to be £350k in year 1 and £1.373m in year 5. As no other drugs were assumed to be displaced, the net medicines budget impact is expected to remain as £350k in year 1 and £1.373m in year 5.

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

The undernoted references were supplied with the submission. The references shaded in grey are additional to those supplied with the submission.


5. www.clinicaltrials.gov [Identifiers: NCT00561470, NCT01571284, NCT01670721]


This assessment is based on data submitted by the applicant company up to and including 10 January 2014.

*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

Drug 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 drug 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.