

Public Summary Document

Product: Aflibercept, solution for IV injection, 100 mg/4 mL and 200 mg/8 mL, Zaltrap[®]

Sponsor: Sanofi-Aventis Australia

Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission sought a Section 100 (Efficient Funding of Chemotherapy) Authority required (Streamlined) PBS listing for the treatment, in combination with an irinotecan-fluoropyrimidine-based chemotherapy, of a patient with previous treatment with an oxaliplatin-based chemotherapy regimen for metastatic colorectal cancer (mCRC) with a WHO performance status of 0 or 1.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This was the first consideration by the PBAC of aflibercept for mCRC.

Aflibercept 4 mg/0.1 mL injection is currently PBS-listed for subfoveal choroidal neovascularisation due to age-related macular degeneration.

3. Registration Status

Aflibercept was TGA registered on 2nd April, 2013 for the following indication:

‘Zaltrap[®] (aflibercept) in combination with irinotecan-fluoropyrimidine-based chemotherapy is indicated in adults with metastatic colorectal cancer previously treated with an oxaliplatin-containing regimen.’

4. Listing Requested and PBAC’s View

Section 100 (Efficient Funding of Chemotherapy)

Private Hospital/Private Clinic Authority required

Public Hospital Authority Required (STREAMLINED)

Initial PBS-subsidised treatment, in combination with an irinotecan-fluoropyrimidine-based chemotherapy, of a patient with previous treatment with an oxaliplatin-based chemotherapy regimen for metastatic colorectal cancer with a WHO performance status of 0 or 1.

Continuing PBS-subsidised treatment, in combination with an irinotecan-fluoropyrimidine-based chemotherapy, of a patient with metastatic colorectal cancer who has previously received PBS-subsidised treatment with aflibercept and who does not have progressive disease and who remains on an irinotecan-fluoropyrimidine-based chemotherapy.

The PBAC noted that the proposed listing would allow aflibercept to be used in a first, second or even a third and subsequent line setting following failure with a bevacizumab-oxaliplatin containing chemotherapy regime (first line therapy), and, cetuximab monotherapy or cetuximab-irinotecan containing chemotherapy regimen (second line therapy). Use of aflibercept in a first line or third line setting was a concern to the PBAC because the trial data presented in the submission did not examine aflibercept’s use in such settings – there was no

comparison to bevacizumab (first line treatment) and the inclusion criteria of the trials meant that the trials were not limited to patients who had failed to 2 lines of therapy (third line setting). The PBAC was also concerned that the proposed listing would push cetuximab use from its current second line setting to a third line setting despite cetuximab having demonstrated cost-effectiveness in the second line setting. The PBAC noted the sponsor's argument that aflibercept would be unlikely to be used in a third line setting because such patients would be expected to have a WHO performance status of 2 or more by that stage and not 0 or 1 as requested in the restriction, and, unlikely to be used in the first line setting because bevacizumab is well established as first-line treatment. However, the PBAC still considered the requested listing to be unjustified based on the evidence presented in the submission.

5. Clinical Place for the Proposed Therapy

Aflibercept is an angiogenesis inhibitor that acts as a VEGF 'trap' by acting as a decoy VEGF receptor. The current treatment algorithm for colorectal cancer is dependent on K-RAS status, with cetuximab being available to those with wild-type (WT) K-RAS in a second line setting. Bevacizumab added to chemotherapy is currently PBS listed for use as first line therapy. Several first line therapies/chemotherapy regimens do not contain oxaliplatin, for instance single agent fluorouracil (5FU) or capecitabine, or combinations of irinotecan and 5FU.

Aflibercept was proposed by the submission for use with irinotecan-fluoropyrimidine-based chemotherapy as second-line therapy after failure on oxaliplatin-based chemotherapy in the first line, in both patients with WT K-RAS and K-RAS mutant mCRC. The submission expected aflibercept to be used in a sequential manner – clinicians would use bevacizumab + chemotherapy first, then aflibercept + chemotherapy, then cetuximab+chemotherapy (in K-RAS wild type mCRC).

The PBAC noted the evolving nature of mCRC treatment and the inherent lack of clarity in the clinical place of aflibercept in the treatment of mCRC. Consequently, the alignment of the proposed listing and the clinical place of aflibercept in the treatment of mCRC would continue to be informed by future practice trends and new clinical trial data.

6. Comparator

The submission nominated the combination regimen of folinic acid, fluorouracil and irinotecan (FOLFIRI) alone as the main comparator for patients with K-RAS mutant tumours, and, cetuximab as the main comparator for patients with WT K-RAS tumours.

The PBAC did not accept the sole comparison to FOLFIRI in the K-RAS mutant patient population as being appropriate for the requested PBS listing. The PBAC noted that a range of chemotherapy regimens are used equally and that current data shows the add-on benefit of biological agents such as VEGF inhibitors depends on what chemotherapy agents they are combined with and what line of therapy (i.e. first line, second line, third line etc) they are used in. Therefore, the PBAC considered that a comparison limited to FOLFIRI in the K-RAS mutant patient population was not fully informative in assessing the incremental benefit of aflibercept for the treatment of mCRC.

The PBAC accepted that FOLFIRI (in K-RAS mutant tumours) and cetuximab (in WT K-RAS tumours) are relevant comparators, but considered that a comparison against panitumumab (recommended for PBS listing in March 2013 as second line therapy after failure of first-line chemotherapy in WT-KRAS tumours but yet to be PBS listed) would also be relevant.

The PBAC further considered that aflibercept may also substitute for the chemotherapy regimens of folinic acid, fluorouracil plus oxaliplatin (FOLFOX) or capecitabine with oxaliplatin (XELOX) if the combination of single agent fluorouracil or capecitabine with bevacizumab is used as first line therapy. For all of these options, the PBAC considered that it is likely that aflibercept will add to the current chemotherapy regimens rather than displace them entirely, so a comparison of aflibercept in combination with FOLFOX or XELOX against FOLFOX or XELOX alone respectively would be relevant.

7. Clinical Trials

For patients with K-RAS mutant tumours the submission presented one double-blind randomised trial (VELOUR) comparing aflibercept + FOLFIRI with placebo + FOLFIRI in 1,226 patients with mCRC, who had progressed after prior therapy with oxaliplatin.

For patients with WT K-RAS tumours, the submission presented an indirect comparison comparing aflibercept to cetuximab using the VELOUR trial and an open-labelled RCT, EPIC. The EPIC trial compared cetuximab plus irinotecan with irinotecan alone in 1,298 patients with mCRC, who have had prior therapy with oxaliplatin. As not all of the 1,298 patients had WT K-RAS tumours, the indirect comparison was based on a post-hoc sub-group analysis of 192 patients from EPIC with a known WT K-RAS status.

A summary of the published randomised trials presented in the submission is shown in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
VELOUR		
Van Cutsem E. et al.	<p>A Multinational, Randomized, Double-blind Study, Comparing the Efficacy of Aflibercept Once Every 2 Weeks versus Placebo in Patients with Metastatic Colorectal Cancer (mCRC) Treated with Irinotecan / 5-FU Combination (FOLFIRI) after Failure of an oxaliplatin based regimen. STUDY NUMBER: EFC10262</p> <p>Aflibercept EVD Addendum: Report created by Sanofi Global Evidence Value Development (EVD) containing: Post-hoc analyses commissioned by Sanofi Global Medical Re-analyses requested by Sanofi Australia for PBAC submission.</p> <p>Addition of Aflibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal</p>	Journal of Clinical Oncology 2012. 30 (28): 3499-3506

	Cancer Previously Treated With an Oxaliplatin-Based Regimen.	
Van Cutsem E. et al.	Intravenous (IV) aflibercept versus placebo in combination with irinotecan/5-FU (FOLFIRI) for second-line treatment of metastatic colorectal cancer (mCRC): Results of a multinational phase III trial (EFC10262-VELOUR)	Ann Oncol, 2011, 22 suppl 5 (ESMO-World Congress on Gastrointestinal Cancer) Barcelona, Abstract No: O-0024 (ESMO 13th World Congress on Gastrointestinal Cancer 22–25 June 2011)
Tabernero J et al.	Results from VELOUR, a Phase 3 Study of Aflibercept versus Placebo in combination with FOLFIRI for the treatment of patients with previously treated metastatic colorectal cancer. Results from pre-specified subgroup analyses.	EMCC 2011, Stockholm, Sweden. Abstract 6LBA ASCO 2012, Chicago, Illinois, USA. Abstract 3602.
Joulain F et al.	Aflibercept/FOLFIRI vs. placebo/FOLFIRI in metastatic colorectal cancer (mCRC): post-hoc analysis of survival excluding adjuvant-only patients in the VELOUR trial.	ASCO 2012, Chicago, Illinois, USA. Abstract 3505
Allegra et al.	Effects of prior bevacizumab (B) use on outcomes from the VELOUR study: A phase III study of aflibercept (Afl) and FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC) after failure of an oxaliplatin regimen.	ASCO 2012, Chicago, Illinois, USA. Abstract 3505
Ruff P et al.	Analysis of overall survival and safety during the course of the phase III VELOUR trial comparing FOLFIRI and aflibercept or placebo in patients with mCRC that progressed on prior oxaliplatin treatment.	ASCO GI 2013. J Clin Oncol 30: 2012 (suppl 34; abstr 451).
Ferry D et al.	On-treatment progression-free survival analysis of aflibercept-FOLFIRI treatment within 28 days of progression in metastatic colorectal cancer: Updated efficacy results from the VELOUR study.	ASCO GI 2013. J Clin Oncol 30: 2012 (suppl 34; abstr 469).
Mitchell et al.	North American (NA) subgroup results from VELOUR: Ziv-aflibercept versus placebo (pbo) plus FOLFIRI in mCRC that is resistant to or has progressed after an oxaliplatin-containing regimen.	ASCO GI 2013. J Clin Oncol 30: 2012 (suppl 34; abstr 465).
EPIC		
NCT00063141	Phase III Randomized, Open-Label, Multicenter Study of Irinotecan and Cetuximab vs. Irinotecan as Second-Line Treatment in Patients with Metastatic, EGFR-Positive Colorectal Carcinoma. 2007	

Sobrero A et al.	EPIC: Phase III Trial of Cetuximab Plus Irinotecan After Fluoropyrimidine and Oxaliplatin Failure in Patients With Metastatic Colorectal Cancer.	J Clin Oncol 2008; 26:2311-2319
Langer C et al.	Analysis Of K-ras Mutations In Patients With Metastatic Colorectal Cancer Receiving Cetuximab In Combination With Irinotecan: Results From The Epic Trial.	Annals Oncol. 2008; 19 (S*): viii133 (385P)
Sobrero A et al.	Scheithauer W, Maurel J, et al. Cetuximab Plus Irinotecan for Metastatic Colorectal Cancer (mCRC): Safety Analysis of the first 400 Patients in a Randomized Phase III Trial (EPIC) [abstract].	Annual Meeting Proceedings of the American Society of Clinical Oncology 2005; 23: 266
Abubakr Y et al.	Cetuximab plus irinotecan for metastatic colorectal cancer (mCRC): Safety analysis of 800 patients in a randomized phase III trial (EPIC).	Journal of Clinical Oncology: ASCO annual meeting proceedings 2006; 24: 3556.

Abbreviations: AFL, aflibercept; FOL, FOLFIRI; IRI, irinotecan, CTX; cetuximab; IV, intravenous; LV, leucovorin; 5-FU. 5-fluorouracil

The PBAC noted the lack of a common comparator in the indirect comparison.

8. Results of Trials

The results of the VELOUR trial are shown in the table below.

Results of OS and PFS across the direct randomised trials

VELOUR	Aflibercept + FOLFIRI n with event/N (%) [or mean ± SD]	Placebo + FOLFIRI n with event/N (%) [or mean ± SD]	Absolute difference RD [or median difference] (95% CI)	Relative difference HR (95% CI)
Primary outcome: Number of death events	403/612 (65.8%)	460/614 (74.9%)	-0.09 (-0.14,-0.04)*	0.817 (0.714,0.935)
Median OS (mths)	13.50 (12.517 – 14.949)	12.06 (11.072 – 13.076)	1.44	
Secondary outcome: Number of progression events.	393/612 (64.2%)	454/614 (73.9%)	-0.10 (-0.15,-0.05)*	0.758 (0.661, 0.869)
Median PFS (mths)	6.90 (6.51 – 7.20)	4.67 (4.21 – 5.36)	2.23	

SD = standard deviation; HR = hazard ratio; OS = overall survival; PFS = progression free survival

*Calculated as a part of the evaluation

The PBAC was not convinced that the results of the VELOUR trial were suitable for estimating the effectiveness of aflibercept in patients with K-RAS mutation, as VELOUR included patients with both WT K-RAS and K-RAS mutation. K-RAS status was not determined in VELOUR and therefore a post-hoc analysis was not possible. Despite the arguments noted in the sponsor's pre-sub-committee response, the PBAC considered that

there was insufficient evidence to conclude that K-RAS status is not an effect modifier of aflibercept, although this issue was of a less concern to the PBAC than the magnitude of overall survival (OS) gain.

The PBAC considered a median 1.44 months survival gain to be modest and the clinical relevance and importance to be doubtful. The PBAC noted that an American Society of Clinical Oncology statement recently reported that in the mCRC setting, a meaningful improvement is 3-5 months. The PBAC recalled that in recommending cetuximab for PBS listing in WT-KRAS tumours as second line treatment, the CO.17 study (the key evidence of the submission) reported a survival gain of 4.7 months.

The submission estimated a mean 2.9 months survival gain and argued that a mean survival gain is a more relevant result than median overall survival gain. The PBAC considered that mean survival would be more persuasive if it was a directly measured value and not an estimated value.

For the indirect comparison of aflibercept versus cetuximab (WT K-RAS). Only hazard ratios for OS and progression free survival (PFS) were calculated by the submission. The submission did not calculate or report relative risks, odds ratios or risk differences for the indirect comparison. Results of the indirect comparison are shown in the tables below.

Summary of results of the indirect comparison – OS hazard ratios

VELOUR				EPIC			
Trial ID	Treatment effect ^a HR (95% CI)	Aflibercept + FOLFIRI (months)	Placebo + FOLFIRI (months)	Irinotecan (months)	Cetuximab + Irinotecan (months)	Treatment effect ^b HR (95% CI)	Indirect estimate of effect ^c Indirect HR (95% CI)
		n=612	n=614	n=95	n=97		
VELOUR	0.817 (0.714,0.935)	13.50	12.06				
EPIC				11.56	10.94	1.29 (0.89,1.85)	0.63 (0.429, 0.935)

CI = confidence interval; HR = hazard ratio

a proposed drug over common reference, **b** main comparator over common reference

c inferred as proposed drug over main comparator

Summary of results of the indirect comparison – PFS hazard ratios

VELOUR				EPIC			
Trial ID	Treatment effect ^a HR (95% CI)	Aflibercept + FOLFIRI (months)	Placebo + FOLFIRI (months)	Irinotecan (months)	Cetuximab + Irinotecan (months)	Treatment effect ^b HR (95% CI)	Indirect estimate of effect ^c Indirect HR (95% CI)
		n=612	n=614	n=95	n=97		
VELOUR	0.758 (0.661, 0.869)	6.9	4.67				
EPIC				2.79	3.98	0.77 (0.57, 1.04)	0.98 (0.708, 1.370)

CI = confidence interval; HR = hazard ratio

a proposed drug over common reference, **b** main comparator over common reference

c inferred as proposed drug over main comparator

The submission claimed that the results indicate aflibercept and cetuximab provide similar efficacy in the second line mCRC treatment setting in terms of progression free survival, and better efficacy results favouring aflibercept based on OS gain.

The PBAC noted that there were several significant limitations in the exchangeability of the trials used in the indirect comparison. These limitations were:

- No crossover in the VELOUR trial and a high rate of crossover in the EPIC trial. This was likely to underestimate the effect of the cetuximab arm and bias the results of the indirect comparison in favour of aflibercept.
- There were differences in the baseline characteristics between the two trials (Eastern Cooperative Oncology Group (ECOG) performance status, prior bevacizumab use and line of therapy)
- The hazard ratio from the VELOUR trial was based on a pooled estimate using WT K-RAS and K-RAS mutant patients, whereas the hazard ratio in EPIC was based on WT K-RAS patients only.
- The results from the EPIC trial used in the indirect comparison were based on a sub-group analysis with small patient numbers and as such were likely to have insufficient power to detect changes in OS or PFS.

As a result of these limitations, the PBAC found it difficult to make comparisons across the trials and therefore was not confident in judging the comparative effect of aflibercept with cetuximab.

With regard to comparative harms, a difference of greater than or equal to 2% between the two treatment arms in VELOUR for Grade 3-4 adverse events was reported for hypertension, diarrhoea, stomatitis and ulceration, asthenic conditions, GI and abdominal pains, dehydration and palmar-plantar erythrodysesthesia syndrome. The PBAC noted that aflibercept was associated with increased chemotherapy-related toxicity when added to FOLFIRI.

The submission did not conduct a formal indirect comparison of adverse events. The Pre-Sub-Committee Response acknowledged the different side effect profile of aflibercept and cetuximab and noted that cetuximab is associated with more diarrhoea, nausea and vomiting adverse events and aflibercept is associated with more asthenic conditions and neutropaenia.

9. Clinical Claim

For the K-RAS mutant patient population, the submission described aflibercept plus FOLFIRI as superior in terms of comparative effectiveness and inferior in terms of comparative safety over FOLFIRI alone. The PBAC considered this claim reasonable, although noted that the median overall survival gain of 1.44 months was modest.

For the WT K-RAS patient population, the submission described aflibercept plus FOLFIRI as non-inferior in terms of comparative effectiveness over cetuximab (either as mono-therapy or in combination with an irinotecan-based regimen). The PBAC did not accept this claim for reasons relating to the limitations in the exchangeability of the trials as outlined under 'results of trials'.

There was an implicit assumption in the submission that aflibercept is non-inferior to cetuximab in terms of comparative safety. The PBAC did not agree that this was a reasonable assumption, and considered aflibercept to be potentially worse than cetuximab in terms of comparative harms.

10. Economic Analysis

The submission presented two economic evaluations based on the following patient populations:

- 1) K-RAS mutant patients (40% of mCRC population). A modelled cost-utility analysis based on the claim of superior efficacy and inferior safety using the direct randomised trial, VELOUR, was presented. The submission calculated an ICER between \$45,000 - \$ 70,000/QALY and less though in the same range per LYS based on PFS and OS results from VELOUR, extrapolated to 5 years duration (from 18 months (PFS) and 2 years (OS) of trial data) and applying utility weights for progression free and progressed health states, with decrements for progression and adverse events.
- 2) WT K-RAS patients (60% of mCRC population). This was a cost-minimisation analysis based on the non-inferiority claim for PFS, using an indirect comparison of randomised trials and including additional costs for administration and adverse events.

The PBAC noted that that at least 43.9% of the life year gains and 52.1% of the QALY gains associated with aflibercept treatment were accumulated during the extrapolation period, and so the extrapolation of OS was the main driver of the economic model. The PBAC observed that the extrapolation of OS beyond the trial period reduced the final calculated ICER from greater than \$200,000/QALY to \$45,000-\$70,000/QALY and greater than \$200,000/LYS to \$45,000-\$70,000/LYS, which indicated to the PBAC that the survival benefits from the trial were greatly enhanced by assumed future benefits. It was not possible to test the uncertainty around the assumed modelled estimates for overall survival. As a result, the PBAC considered that it was plausible that the true ICER could be between \$45,000-\$70,000/QALY or \$45,000-\$70,000 /LYS. The PBAC further noted that this did not compare favourably to the ICER calculated for cetuximab (for both a comparison of cetuximab versus best supportive care and cetuximab versus FOLFIRI) when cetuximab was recommended for PBS listing.

The PBAC considered the ICER between \$45,000-\$70,000/QALY or \$45,000-\$70,000 /LYS to be unacceptably high, particularly in the context of an end-of-life treatment and in which there are existing treatments that appear to give better results.

For the cost-minimisation analysis in the WT K-RAS patient population, the PBAC noted that the use of weighting by indication to calculate a weighted price for aflibercept effectively increased the price due to price parity with cetuximab. The PBAC considered this approach to be unjustified as the PBAC considered that non-inferiority to cetuximab had not been adequately established.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost per year to the PBS /RPBS of between \$10 – \$30 million in Year 5.

The PBAC noted that the submission used an incidence approach to determine patient numbers and was concerned that this approach does not account for uptake by the prevalent pool of patients who would be ready to receive second or subsequent line therapy at the time of listing. These patients would be eligible to receive aflibercept under the proposed listing. This would in turn underestimate patients eligible to receive aflibercept and would have the greatest effect in the first year of listing. Additionally, the estimated number of patients receiving chemotherapy and oxaliplatin-based chemotherapy was likely to have been underestimated, resulting in a further underestimation of eligible patients and costs. Overall, the PBAC considered that under the proposed listing, the potential for aflibercept to replace bevacizumab as first line treatment, delay treatment of current second line treatments (such as cetuximab) rather than substitute for them, and, be used in third line treatment, the total budgetary consequence of listing aflibercept is likely to be underestimated.

The PBAC noted the sponsor's proposal to enter into a special pricing arrangement.

12. Recommendation and Reasons

The PBAC rejected the submission on the basis of inadequate comparative efficacy and potentially worse safety resulting in an unacceptably high ICER, a lack of clarity regarding the clinical place in therapy of aflibercept, an absence of comparative data against other relevant chemotherapy regimens, and, on the basis that non-inferiority against cetuximab and panitumumab had not been adequately established.

The PBAC considered that further head-to-head data that quantifies the incremental benefit of adding aflibercept to different chemotherapy regimens commonly used to treat mCRC would be informative, given the PBAC's concern over the small magnitude of overall survival gain reported in the VELOUR trial, and, the PBAC's awareness that the benefit of biological agents can vary depending on the chemotherapy regimen that they are given in combination with and the line of therapy (i.e. first line, second line, third line etc.) that they are used in. A comparison to panitumumab would also be considered relevant.

The PBAC advised that any resubmission would need to be considered as a major submission.

Outcome:

Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor is disappointed by the PBAC's decision and disagrees with several comments. In particular, the sponsor disagrees with comparing aflibercept's overall survival benefit in the actively controlled, second-line VELOUR trial (aflibercept + FOLFIRI vs. FOLFIRI alone) to the survival benefit achieved by cetuximab in the placebo-controlled, third-line CO.17 trial (cetuximab + best supportive care vs. best supportive care alone). The sponsor also disagrees

with the statement aflibercept is potentially worse than cetuximab in terms of comparative harms. Sanofi believes that it is the remit of the clinician to assess the risk benefit profile of a product for their individual patients. Whilst appreciating the Committee's concerns about the high ICER, the sponsor believes that Zaltrap does provide clinicians with another option for the treatment of mCRC patients in Australia and therefore remains committed to working with the PBAC to enable access to Zaltrap.