Aberdeen HTA Group

Aflibercept for treating diabetic macular oedema

Critique of dexamethasone and fluocinolone economic data and additional exploratory subgroup analyses based on CRT level

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This document contains i) a summary of the critique of dexamethasone and fluocinolone economic data; ii) a critique of dexamethasone and fluocinolone economic data reported in the company's submission; iii) a summary of the exploratory subgroup analyses based on central retinal thickness (CRT) level; iv) additional exploratory subgroup analyses based on CRT level requested during the PMB for this appraisal, which took place on Wed 7 January 2015.

i. SUMMARY OF THE CRITIQUE OF DEXAMETHASONE AND FLUOCINOLONE ECONOMIC DATA

With regard to the comparison between aflibercept and intravitreal corticosteroids (i.e dexamethasone intravitreal implant and fluocinolone acetodine intravitreal implant), the ERG highlight the following issues:

- Used of corticosteroids is likely to be restricted to patients insufficiently responsive to other therapies and/or pseudophakic;

- It is likely that corticosteroids are considered after laser and anti-VEGF treatments in the DMO clinical pathway;

- Indirect comparisons between aflibercept and corticosteroids were limited by the dearth of available evidence;

- Only one study comparing dexamethasone plus laser versus laser alone was available for inclusion in the network meta-analysis (NMA);

- No indirect comparison between aflibercept and fluocinolone was possible due to the lack of a common comparator;

- In the company's economic model the inputs for the comparison between aflibercept and corticosteroids were derived from the VISTA/VIVID trial for aflibercept, the PLACID trial for dexamethasone and the FAME study for fluocinolone;

- For some efficacy and safety endpoints as no other evidence was available the company assumed equivalence between dexamethasone and fluocinolone to laser. Whether this assumption is reasonable and trustworthy is open to question;

- The ERG have revised the submitted modelling for the comparisons with dexamethasone and with fluocinolone to take into account the main ERG concerns;

- The submitted model suggests that aflibercept dominates dexamethasone, while the ERG revisions suggest a cost effectiveness of £2,872 per QALY;

- The submitted model and the ERG revised model suggest that aflibercept dominates fluocinolone if there is no fluocinolone PAS. The ERG revised model suggests dominance continues up to a fluocinolone PAS of 20%, with a fluocinolone PAS of 75% resulting in a cost effectiveness estimate of £20,990 per QALY;

- For the pseudophakic subgroup the submitted model and the ERG revised model suggest that aflibercept dominates fluocinolone if there is no fluocinolone PAS. The ERG revised model suggests dominance continues up to a fluocinolone PAS of 20%, with a fluocinolone PAS of 80% resulting in a cost effectiveness estimate of £19,722 per QALY.

ii. CRITIQUE OF DEXAMETHASONE AND FLUOCINOLONE ECONOMIC DATA

The company maintains that the use of intravitreal corticosteroids for the treatment of DMO is restricted to people insufficiently responsive to non-steroids therapies and/or pseudophakic eyes. Dexamethasone intravitreal implant is licensed in adults with DMO who are pseudophakic or who are insufficiently responsive to or unsuitable for non-corticosteroid therapies. Fluocinolone acetonide intravitreal implant is recommended (TA301) for the treatment of adults with chronic DMO insufficiently responsive to available therapies or who are pseudophakic.

Indirect comparisons with corticosteroids were hampered by the lack of studies with common comparators (laser) and by the differences in efficacy outcomes, duration, and characteristics of patient population between studies. The company include for completeness an exploratory economic analysis of aflibercept versus intravitreal corticosteroids (i.e. dexamethasone and fluocinolone) but highlight that this was limited by the absence of robust comparative data on efficacy and safety and by the uncertainty regarding the current position of corticosteroids in the DMO clinical pathway.

For the indirect comparison of aflibercept versus dexamethasone the company included one RCT (PLACID), which randomised a total of 253 patients with diffuse DMO to 0.7mg dexamethasone implant at baseline plus laser at month 1 or to sham implant at baseline and laser at 1 month and assessed outcomes at 12 months. An indirect comparison between aflibercept and fluocinolone was not possible because the identified FAME RCT did not include a common comparator. FAME assessed the efficacy and safety of intravitreal implants releasing fluocinolone in patients with persistent DMO despite ≥1 macular laser treatment over a 3-year period. A total of 956 patients were randomised to 0.2µg/day fluocinolone implant or 0.5µg/day fluocinolone implant, or sham injection.

The company present the inputs and assumptions of the economic model for the comparison of aflibercept versus dexamethasone in Table 117 of the submission and for the comparison aflibercept versus fluocinolone in Table 120.

The PLACID trial provides the source data for the outcome 'gain ≥10 letters'. The probabilities for laser therapy were estimated from the VIVID/VISTA trial (Table 71 of the company's submission). The probabilities for dexamethasone were estimated by applying the relative risk (RR) versus laser based on the network meta-analysis (NMA). No data were available from the PLACID trial for the visual outcomes of gaining >= 15 letters, losing ≥10, and losing ≥15 letters. Therefore, the probabilities for these efficacy

outcomes were assumed to be the same as those of laser based on the results of the VIVID/VISTA trial (Table 71 of the company's submission).

For the comparison between fluocinolone and laser, the FAME trial provides the source data for the outcome 'gain of ≥15 letters' and for the relevant safety outcomes. Probabilities for the other efficacy outcomes were assumed to be equivalent to the laser arm of the VIVID/VISTA trial.

In both cases, the ERG have concern over the use of probabilities from the laser arm of the VIVID/VISTA trial to estimate effectiveness of dexamethasone and fluocinolone as this assumes equal efficacy between laser and corticosteroids. Whether this assumption is valid is open to discussion.

The ERG confirms that for both the comparison of aflibercept with dexamethasone and the comparison of aflibercept with fluocinolone:

- the clinical effectiveness estimated used are as per Table 25 and Table 26 of the ERG report
- the dosing and monitoring estimates used as per Table 34 of the ERG report.

The other assumptions underlying this modelling are as outlined in Section 5.2 of the ERG report.

Table 1: Monthly transition probabilities for the first year

	+2HS	+1HS	-1HS	-2HS
All patients				
Aflibercept	2.08%	3.51%	[redacted]	0.02%
Fluocinolone	1.62%	1.70%	1.28%	0.78%
Pseudophakic				
Aflibercept	2.08%	3.51%	[redacted]	0.02%
Fluocinolone	1.62%	1.31%	1.28%	0.78%

These values are taken directly from the submitted electronic model of the company, though they do not match exactly those reported in Table 25. Consequently, the data for aflibercept and those drawn from the laser arm of the VIVID/VISTA trial may not be specific to the pseudophakic subgroup within the submitted electronic model.

The SmPC suggests that dexamethasone may be re-administered after around 6 months if there is decreased vision or thickening of the retina due to DMO. The PLACID trial saw an implant at baseline being followed by retreatment at 6 months for 58% and at 9 months for 7% during the 12 months of the

trial. The current submission assumes three administrations in the first year, followed by two in each of the subsequent two years and none thereafter to give a total of 7 over the assumed five year treatment period. Each administration has a direct drug cost of £870 as drawn from the BNF.

The TA301 fluocinolone in DMO assumed that fluocinolone would be administered every three years among those remaining on treatment, presumably due to the FAME trial being of three-year duration. The SmPC suggests an additional implant may be considered after 12 months. The FAME trial saw similar retreatment rates in the two fluocinolone arms. In the low-dose fluocinolone arm, 74% of participants received one dose, 22% received two doses and 4% received three or more doses. In the high-dose arm 71% of participants received one dose, 23% received two doses and 6% received three or more doses. The current submission suggests an administration in the first year and another in the third year, which compresses the administration schedule compared to that assumed within the company submission for TA301, but still results in two administrations during the five year treatment period of the model. Each administration has a direct drug cost, exclusive of any PAS, of £5,500 as drawn from the BNF.

The company cost effectiveness estimates of the written submission are as per Tables 43, 44, 45, 46, and 47 of the ERG report. The cost effectiveness estimates of the submitted electronic model differ slightly from these. The results of the submitted electronic model are presented below.

The ERG revisions to the costs of blindness had the main impact upon results for the comparisons with laser and ranibizumab, with the rate of change off treatment and the DMO mortality multiplier also having an impact. Due to time constraints it has not been possible to apply all the revisions to the company model outlined in the ERG report for the comparisons with dexamethasone and fluocinolone. All that have been implemented for the exploratory analyses comparing aflibercept with dexamethasone and fluocinolone, as outlined in the footnotes to Section 5.4 of the ERG report, are:

- revising the discounting formulae;
- discounting the costs of blindness;
- changing annual cost of blindness to £7,429;
- changing the cost of blindness within the model to be a monthly cost of blindness;
- revising the quarterly rate of worsening off treatment to 1%; and ,
- applying a 2.45 DMO mortality multiplier.

Table 2: Cost effectiveness results versus with dexamethasone

	Aflibercept	Dexamethasone	Net
Submitted model			
Costs	[redacted]	[redacted]	-£10,251
QALYs	7.689	7.301	0.388
ICER			Dominant
Submitted model: revised			
Costs	[redacted]	[redacted]	£1,050
QALYs	7.522	7.156	0.365
ICER			£2,872

Table 3: Cost effectiveness results versus with fluocinolone: all patients

	Aflibercept	Fluocinolone	Net
Submitted model			
Costs	[redacted]	[redacted]	-£14,510
QALYs	7.705	7.367	0.338
ICER			Dominant
Submitted model: revised			
Costs	[redacted]	[redacted]	-£3,076
QALYs	7.536	7.224	0.312
ICER			Dominant

Table 4: Cost effectiveness results versus fluocinolone: all patients: revised model: fluo. PAS

Δ QALYs	Fluo. PAS	Δ Costs	ICER	Fluo. PAS	Δ Costs	ICER
0.0919	5%	-£2,435	Dominant	55%	£3,981	£12,763
	10%	-£1,793	Dominant	60%	£4,623	£14,819
	15%	-£1,152	Dominant	65%	£5,265	£16,876
	20%	-£510	Dominant	70%	£5,906	£18,933
	25%	£132	£422	75%	£6,548	£20,990
	30%	£773	£2,479	80%	£7,189	£23,046
	35%	£1,415	£4,536	85%	£7,831	£25,103
	40%	£2,057	£6,592	90%	£8,473	£27,160
	45%	£2,698	£8,649	95%	£9,114	£29,217
	50%	£3,340	£10,706	100%	£9,756	£31,273

Table 5: Cost effectiveness results versus with fluocinolone: pseudophakic

	Aflibercept	Fluocinolone	Net
Submitted model			
Costs	[redacted]	[redacted]	-£15,893
QALYs	7.738	7.344	0.394
ICER			Dominant
Submitted model: revised			
Costs	[redacted]	[redacted]	-£3,093
QALYs	7.567	7.203	0.364
ICER			Dominant

Table 6: Cost effectiveness results versus with fluocinolone: pseudophakic: revised model: fluo. PAS

Δ QALYs	Fluo. PAS	Δ Costs	ICER	Fluo. PAS	Δ Costs	ICER
0.0919	5%	-£2,451	Dominant	55%	£3,965	£10,902
	10%	-£1,809	Dominant	60%	£4,607	£12,666
	15%	-£1,168	Dominant	65%	£5,248	£14,430
	20%	-£526	Dominant	70%	£5,890	£16,194
	25%	£115	£318	75%	£6,532	£17,958
	30%	£757	£2,082	80%	£7,173	£19,722
	35%	£1,399	£3,846	85%	£7,815	£21,486
	40%	£2,040	£5,610	90%	£8,456	£23,250
	45%	£2,682	£7,374	95%	£9,098	£25,014
	50%	£3,324	£9,138	100%	£9,740	£26,778

iii. SUMMARY OF THE EXPLORATORY SUBGROUP ANALYSES BY BASELINE CENTRAL RETINAL THICKNESS (CRT)

- Using information provided by the manufacturer at clarification, based upon the VIVID/VISTA trial data, the fully revised ERG model suggests a cost effectiveness for aflibercept versus laser of:
  - £28,503 per QALY across all patients
  - £21,958 per QALY for those with a CRT ≥ 400μm at baseline
  - £28,503 per QALY for those with a CRT < 400μm at baseline

- The cost effectiveness estimates worsen considerably if the VIVID/VISTA EQ-5D general estimating equations (GEE) utility function is applied.

iv. EXPLORATORY SUBGROUP ANALYSES BY BASELINE CRT

The company CRT ≥ 400µm subgroup analysis only revised the probabilities in the laser arm and not the clinical effectiveness estimates for aflibercept versus laser. Data supplied at clarification suggests the following subgroup specific laser probabilities of improving and worsening within the VIVID/VISTA trial data.

Table 7: Monthly probabilities of gaining and losing letters in the laser arm of VIVID/VISTA

	All patients	CRT ≥400µm	CRT <400µm
Gain 10 letters	0.01697	[redacted]	[redacted]
Lose 10 letters	[redacted]	[redacted]	[redacted]
Gain 15 letters	0.00674	[redacted]	[redacted]
Lose 15 letters	0.00781	[redacted]	[redacted]

Further data supplied during the clarification process suggest the following subgroup specific relative risks within the VIVID/VISTA data.

Table 8: Relative risks of gaining 10 letters VIVID/VISTA

	Aflibercept		Laser				
	n	N	n	N	Weight	RR	RR CI
All patients							
VISTA	88	151	30	154	49%	2.99	[2.11, 4.24]
VIVID	72	135	34	132	51%	2.07	[1.49, 2.88]
Pooled		286		286	100%	**2.48**	[1.73, 3.56]
CRT < 400µm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT ≥ 400µm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9: Relative risks of gaining 15 letters VIVID/VISTA

	Aflibercept		Laser				
	n	N	n	N	Weight	RR	RR CI
All patients							
VISTA	47	151	12	154	50%	3.99	[2.21, 7.23]
VIVID	45	135	12	132	50%	3.67	[2.03, 6.61]
Pooled		286		286	100%	**3.83**	[2.52, 5.81]
CRT < 400µm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT ≥ 400µm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10: Relative risks of losing 10 letters VIVID/VISTA

	Aflibercept		Laser				
	n	N	n	N	Weight	RR	RR CI
All patients							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT < 400µm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT ≥ 400µm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 11: Relative risks of losing 15 letters VIVID/VISTA

	Aflibercept		Laser				
	n	N	n	N	Weight	RR	RR CI
All patients							
VISTA	1	151	14	154	66%	0.07	[0.01, 0.55]
VIVID	0	135	14	132	34%	0.03	[0.00, 0.56]
Pooled		286		286	100%	**0.06**	[0.01, 0.29]
CRT < 400μm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRT ≥ 400μm							
VISTA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VIVID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

These data show a greater relative increase in the likelihood of improvement and a greater relative decrease in the likelihood of worsening among the CRT ≥ 400μm subgroup than among the CRT < 400μm subgroup. While the pattern is consistent and may parallel that for other anti-VEGFs, the point estimates are not statistically significantly different between the subgroups at the 5% level.

It should also be noted that the relative risks derived directly from the VIVID/VISTA trial for aflibercept versus laser differ from those of the NMA.

Table 6: Relative risk point estimates for all patients: VIVID/VISTA vs NMA

	VIVID/VISTA	NMA
Gain 10 letters	2.48	2.07
Gain 15 letters	3.83	3.09
Lose 10 letters	[redacted]	[redacted]
Lose 15 letters	0.06	0.03

Basing the estimates of the relative risks solely upon the VIVID/VISTA data increases the point estimates for the relative risks of gaining letters for aflibercept over laser compared to those of the NMA.

These estimates can be applied within the model[a], coupled with the ERG revisions to the model as outlined within the ERG report Section 5.4[b]. It is worth noting that a number of the remaining elements of the model are not subgroup specific. For instance, the all patient relative risk of discontinuation of the company NMA has been retained for all the following analyses. Dosing as well as the number of laser administrations have also not been made subgroup specific.

Table 7: Cost effectiveness: VIVID/VISTA relative risks and laser probabilities: All patients

	Aflibercept	Laser	Net
Tx. 1st eye	[redacted]	[redacted]	£9,340
Tx. 2nd eye	[redacted]	[redacted]	£4,183
AE 1st eye	[redacted]	[redacted]	-£4
AE 2nd eye	[redacted]	[redacted]	-£5
Fl. Angio.	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£353
Blindness	[redacted]	[redacted]	-£223
Total	[redacted]	[redacted]	£12,938
LYs undisc.	14.245	14.174	0.070
QALYs	7.497	7.043	0.454
ICER			£28,503

[a] Implemented within the *Tx_Input* worksheet by setting cells C14:C17 equal to the subgroup specific values from table 01 and cells C22:C25 equal to the highlighted subgroup specific relative risks of tables 02, 03, 04 and 05.
[b] Coupled with a revision to the baseline DMO FEI to [redacted] as outlined in the main text of Chapter 5 of the ERG report and as per the base case of the ERG revised model of the main ERG report.

Table 8: Cost effectiveness: VIVID/VISTA relative risks and laser probabilities: CRT≥400µm

	Aflibercept	Laser	Net
Tx. 1st eye	[redacted]	[redacted]	£9,365
Tx. 2nd eye	[redacted]	[redacted]	£4,192
AE 1st eye	[redacted]	[redacted]	-£2
AE 2nd eye	[redacted]	[redacted]	-£4
Fl. Angio.	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£348
Blindness	[redacted]	[redacted]	-£261
Total	[redacted]	[redacted]	£12,943
LYs undisc.	14.256	14.170	0.085
QALYs	7.641	7.052	0.589
ICER			£21,958

Table 9: Cost effectiveness: VIVID/VISTA relative risks and laser probabilities: CRT<400µm

	Aflibercept	Laser	Net
Tx. 1st eye	[redacted]	[redacted]	£9,321
Tx. 2nd eye	[redacted]	[redacted]	£4,177
AE 1st eye	[redacted]	[redacted]	-£12
AE 2nd eye	[redacted]	[redacted]	-£6
Fl. Angio.	[redacted]	[redacted]	£0
Visits	[redacted]	[redacted]	-£371
Blindness	[redacted]	[redacted]	-£95
Total	[redacted]	[redacted]	£13,013
LYs undisc.	14.239	14.211	0.028
QALYs	7.447	7.184	0.263
ICER			£49,421

The above estimates are based upon the Czoski-Murray utility function and assume that a change in the BCVA of the WSE has 30% of the quality of life impact of the same change in the BCVA of the BSE. Using the VIVID/VISTA EQ-5D GEE quality of life estimates worsens the cost effectiveness estimates to £102k per QALY, £80k per QALY and £190k per QALY for all patients, the CRT ≥ 400µm subgroup and the CRT < 400µm subgroup respectively.

Due to the pattern of the relative risks being consistent but not significantly different between the subgroups at the 5% level it would be desirable to be able to run the model probabilistically. Unfortunately, the ERG with the information provided in the current submission was unable to run the submitted model probabilistically and obtain sensible estimates within the iterations.