Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema in phakic eyes after an inadequate response to previous treatment (Review of TA613) [ID6307]

Briefing for streamlined cost comparison

For public – contains no information

Chair: Stephen O'Brien and Richard Nicholas

External assessment group: Warwick Evidence

Technical team: Cara Gibbons, Mary Hughes, Ross Dent

Company: Alimera Sciences

Technology details

Fluocinolone acetonide intravitreal implant (FAC) versus dexamethasone intravitreal implant (DEX)

	FAC	DEX
Marketing authorisation	Treatment of vision impairment associated with DMO considered insufficiently responsive to available therapies.	Treatment of adult patients with visual impairment due to DMO who are pseudophakic or who are considered insufficiently responsive to, or unsuitable for non-corticosteroid therapy.
Drug type	Corticosteroid intravitreal implant	Corticosteroid intravitreal implant
Administration	• 1 x implant in affected eye, containing 190 micrograms of FAC, releasing 0.2 micrograms/day for ~36 months. • Possible retreatment after 12 months if patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening DMO. • Administered by intravitreal injection. • Administration in both eyes concurrently is not recommended.	• 1 x implant in affected eye, containing 700 micrograms of DEX. • Possible retreatment after approximately 6 months if patient experiences decreased vision and/or an increase in retinal thickness, secondary to recurrent or worsening DMO. • Administered by intravitreal injection. • Administration in both eyes concurrently is not recommended.
Price	• List price per implant: £5,500 • Has a confidential discount	• List price per implant: £870 per implant. • No commercial arrangement.

Abbreviations: DMO, diabetic macular oedema; FAC, fluocinolone acetonide; DEX, dexamethasone; PAS, patient access scheme

Background

TA301 recommends fluocinolone for people with an intraocular lens (pseudophakic), not in eyes with a natural lens (phakic eye)

This cost comparison reviews the recommendation for phakic eyes – expected publication date: Feb 2024

- Main areas for discussion (changes company base case from cost saving to cost incurring):
    - Time horizon
    - Dosing frequency
    - Subsequent anti-VEGF treatments
- Several complex subgroups of data providing supporting evidence – summarised throughout slides.

Diabetic retinopathy guideline – expected publication date: TBC

- Aim is to publish the outcome of this appraisal before the publication of the new guideline. It will then be incorporated into the new guideline and if a yes, replace the current conclusion on FAC.

Equality considerations raised:

- If a person is registered as blind or partially sighted, they are considered disabled, as stated in the Equality Act 2010 - population in this appraisal is a protected group.

Appraisal history of FAC and DEX

The current appraisal is a part review of TA613. This re-appraisal of FAC (ID6307) and the re-appraisal of DEX in TA824 was prompted by the emergence of RWE

TA301	Fluocinolone acetonide intravitreal implant is recommended as an option for treating chronic DMO that is insufficiently responsive to available therapies only if: • the implant is to be used in an eye with an intraocular (**pseudophakic**) lens
TA613 (part review of TA301)	Fluocinolone acetonide intravitreal implant is **not recommended** as an option for treating chronic diabetic macular oedema that is insufficiently responsive to available therapies in an eye with a natural lens (**phakic eye**).
TA349	Dexamethasone intravitreal implant is recommended for people who have a pseudophakic (intraocular) lens and whose condition did not respond well enough to, or who could not have non-corticosteroid therapy.
TA824 (part review of TA349)	Dexamethasone intravitreal implant is recommended as an option for treating visual impairment caused by diabetic macular oedema in adults only if their condition has not responded well enough to, or if they cannot have non-corticosteroid therapy.

- Review **only** considered evidence and recommendation for people with **a phakic** (natural) lens.
- Replaces TA349 to recommend DEX for whole population, irrespective of having phakic or pseudophakic lens.
- No evidence presented for people who cannot have non-corticosteroid therapy. Expected to be similarly effective, unmet need in this group and low risk to NHS of recommending in this group.

Clinical effectiveness data

Clinical trial evidence

- Trial populations do not match scope population (eyes that have not responded sufficiently to anti-VEGF drugs).
  ↳ Anti-VEGF treatments not widely used at time of RCTs so cannot provide evidence on scope population.
- No statistically significant differences between FAC and sham in phakic only subgroup, but there were between DEX and sham in MEAD TE subgroup (analysis not powered to detect statistically significant differences).

	FAME	MEAD
Treatments	FAC versus sham	DEX versus sham
Trial population	Adults with DMO, BCVA of 20/50 or worse but at least 20/400 and CRT of ≥250 µm by OCT with ≥1 prior macular laser treatment	Adult patients with DMO, BCVA of 20/50 to 20/200 Snellen equivalent, and CRT of ≥300 µm by OCT. People treatment naïve or treatment-experienced (medical or laser therapy).
Phakic subgroups	Treatment-experienced subjects with a phakic lens only.	MEAD treatment experienced subgroup - post hoc analysis of people with phakic and pseudophakic eyes who had received prior treatment before MEAD trial

Real world evidence

- FAC (11 studies [9 with UK sites], 1 meta-analysis, 1 systematic review); DEX (7 studies, [4 with UK sites])
- **EAG:** RWE supports clinical effectiveness of DEX and FAC in people with phakic lens in a population receiving prior anti-VEGF treatments (population within scope). Dosing from RWE used in scenario analyses.
- **EAG:** RWE suggests anti-VEGF drugs used alongside and after FAC/DEX in clinical practice (slide 14).

Technical team: MEAD informed TA824 (DEX) clinical and cost effectiveness estimates for people with phakic and pseudophakic eyes. FAME informed FAC recommendation for pseudophakic eyes.

Indirect treatment comparison: methods

Indirect treatment comparison (ITC)

- Company submission MAIC: treatment experienced people with both phakic and pseudophakic eyes.
- EAG requested phakic MAIC: FAC (FAME phakic-eyes only subgroup) versus DEX (MEAD treatment-experienced subgroup).
- Potential treatment effect modifiers identified by clinicians: duration of DMO, prior DMO treatment, presence of cataract (lens status used as proxy), baseline CRT and baseline BCVA.
- Significantly imbalanced treatment effect modifiers (between overall populations): CRT, lens status and prior DMO treatment
- Base case MAIC: FAME reweighted matched on CRT and lens status and censored at point of additional therapy
    - ESS 119 (86% of pre-weighting) – EAG: loss of sample size when considering phakic-only subgroup of FAME, should be considered when making comparisons with the MEAD-TE subgroup.
    - Large ESS decreases in some outcomes due to missing data. Analysis power compromised = more imprecise results.
- Sham-responses between MEAD and FAME-phakic MAIC were comparable and no significant outcome differences = matching successfully balanced baseline characteristics between 2 sham arms
- Remaining biases because of sampled population differences e.g., retreatment rules (12m vs 6m), allowance of additional therapy, lens status, reweighted characteristics still differ to MEAD.

	FAC	DEX	Company comments
Company MAIC	Adult with persistent DMO despite at least 1 macular laser treatment (n=399)	Post hoc subgroup analysis of adults with phakic and pseudophakic eyes who had received prior treatment (laser or medical treatment) before MEAD trial (n=508)	Limited evidence for DEX in treatment experienced phakic eyes
Phakic MAIC	Post hoc data phakic eyes meeting MEAD inclusion criteria (visual acuity+ central retinal thickness). (n=214)	MEAD TE subgroup (n=508) – same as above.	Analysis guaranteed to present a biased estimate of DEX vs FAC.

Abbreviations: MAIC, matching adjusted indirect comparison; BCVA, best corrected visual acuity; FAC, Fluocinolone Acetonide; DEX, dexamethasone; CRT, central retinal thickness; ESS, effective sample size; TE, treatment-experienced

Indirect treatment comparison: results

EAG: No statistically significant differences between FAC and DEX across all 6 outcomes. Some concerns of bias but concluded FAC and DEX clinically equivalent.

Company: treatment experienced pseudophakic and phakic eyes. Matching on unbalanced TEMs

Outcome	Estimate	CI	P-value	Favoured
Proportion achieving ≥15-letter BCVA improvement from baseline to EOT	2.4	(-8.6, 13.4)	0.667	FAc
Mean change from baseline in BCVA letter score from baseline to EOT	1.6	(-3.3, 6.5)	0.522	FAc
Mean change in CRT from baseline to EOT	-10.9	(-70.9, 48.9)	0.722	DEX
Proportion experiencing serious ocular AEs	-1.4	(-6.6, 3.8)	0.599	FAc
Proportion experiencing IOP-related AEs	-8.0	(-18.5, 2.5)	0.136	FAc
Proportion experiencing cataract-related AEs (in phakic eyes)	-10.5	(-26.6, 5.6)	0.201	FAc

EAG phakic MAIC: FAME phakic eyes and MEAD phakic and pseudophakic eyes. Matching on unbalanced TEMs

Outcome	Estimate	CI	P-value	Favoured
Proportion achieving ≥15-letter BCVA improvement from baseline to EOT	4.0	(-9.09, 17.09)	0.549	FAC
Mean change from baseline in BCVA letter score from baseline to EOT	3.3	(-2.51, 9.11)	0.266	FAC
Mean change in CRT from baseline to EOT	12.0	(-98.50, 122.5)	0.831	FAC
Proportion experiencing serious ocular AEs	-0.1	(-5.98, 5.78)	0.973	FAC
Proportion experiencing IOP-related AEs	-11.8	(-28.37, 4.78)	0.201	FAC
Proportion experiencing cataract-related AEs (in phakic eyes)	-7.5	(-19.84, 4.84)	0.234	FAC

Technical team: Implants have same mechanism of action, based on MAIC conclude clinical equivalence met

Abbreviations: BCVA, best corrected visual acuity; FAC, Fluocinolone Acetonide; DEX, dexamethasone; TE, treatment-experienced; CRT, central retinal thickness; ESS, effective sample size; EOT, end of treatment; IOP, Intraocular Pressure; AE, adverse events; TEM, treatment effect modifier

Dosing

Modelled dosing frequency

Year	FAC		DEX
	Phakic ITC	FAS	
1	[redacted]	[redacted]	1.87
2	[redacted]	[redacted]	1.32
3	[redacted]	[redacted]	0.83
4	[redacted]	[redacted]	1.09
5	[redacted]	[redacted]	1.00
6	[redacted]	[redacted]	0.00
Total	[redacted]	[redacted]	6.11

Company:

- Costs compared over a 6-year time horizon
- Year 1-3: FAME and MEAD; Year 4-6: TA824 for DEX. None assumed for FAC.
- Scenarios: dosing based on RWE (slide 8 & 9).

EAG:

- FAC / DEX dosing may be underestimated.
- Unclear if MEAD and FAME completion rates are sufficiently similar (less in MEAD than FAME) so that their dosing frequencies are comparable.
- Unsure if discontinuation differences due to efficacy/AE or trial protocol differences (e.g., subsequent treatment) and whether this reflects clinical practice.
- Limited data beyond 3 years. Limit time horizon to 3 years?

Technical team:

- EAG's suggestion to limit time horizon to 3 years may be inappropriate.
- NICE methods: time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared.
- TA824 model time horizon was lifetime (40 years) or 10 years (EAG preferred) (cost effective with both).
- NHS RWE suggests FAC dosing lower and DEX dosing similar over 6-year period.
  ↳ Changing time horizon from 6 to 3 years → FAC no longer cost saving

Abbreviation: FAC, Fluocinolone Acetonide; DEX, dexamethasone; RWE, real world evidence

Company RWE dosing scenarios (6-year time horizon)

			DEX			
			MEAD (ITT) permitted re-injection – BASECASE	MEAD (ITT) Evenly spread re-injection intervals	RWE: CHROME (Canada) - True PRN attainable	RWE: Moorfields Eye Hospital UK - Inc. NHS capacity pressures
		TOTAL implants in horizon	6.11	6.11	8.00	6.00
FAC	FAME: Adjusted ITC FAC cohort – BASECASE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	FAME: Unadjusted ITT FAC cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RWE: Medisoft - All NHS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RWE: Birmingham & Midlands Eye Centre (Dobler 2023) - All NHS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	RWE: IRISS - 31/47 NHS centres	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE

Abbreviation: FAC, fluocinolone acetonide; DEX, dexamethasone; RWE, real world evidence; AE, adverse events; SE, standard error

EAG dosing scenario analyses

Cost per eye	FAC	DEX	Net	% change
EAG revised base case	[redacted]	£4,142	[redacted]	-
6-year time horizon (with different injection frequencies for years 4+)				
0.00 yr 4 FAC, 1.00 yr 4&5 DEX	[redacted]	£5,897	[redacted]	112
0.36 yr 4 FAC, 1.00 yr 4&5 DEX	[redacted]	£5,897	[redacted]	60
0.42 yr 4 FAC, 1.00 yr 4&5 DEX	[redacted]	£5,897	[redacted]	52
0.00 yr 4 FAC, 0.82 yr 4&5 DEX	[redacted]	£5,715	[redacted]	96
0.36 yr 4 FAC, 0.82 yr 4&5 DEX	[redacted]	£5,715	[redacted]	44
0.42 yr 4 FAC, 0.82 yr 4&5 DEX	[redacted]	£5,715	[redacted]	35
0.51 yr 4 FAC, [redacted] yr 4&5 DEX	[redacted]	£5,649	[redacted]	16

Abbreviation: FAC, fluocinolone acetonide; DEX, dexamethasone

Additional points raised

Sequencing of treatment

- 8 UK ophthalmologist concensus article proposal: after insufficient response to anti-VEGF drugs, steroid treatment should begin with DEX. If successful and safe, then switch to FAC will reduce treatment burden.
    - If don't respond to DEX, no retreatment and reduced AE risk (e.g., identify people likely to have raised IOP problems).
        - ↳ Effects wear off within months and incur 6 months costs. FAC effects would last 3 years and have 3-year cost.
- Switching RWE in Europe and US (standard practice) suggests DEX benefits are sustained and treatment burden reduced.
- EAG: reasonable evidence to support proposal but not included in company modelling.

Switching to anti-VEGF and other treatments

- Use of non-study treatments was discouraged (FAME) / required withdrawal from study (MEAD)
- RWE suggests subsequent anti-VEGF drugs relatively common on FAC and some evidence for DEX (see back up slide 14)
- Company model does not consider retreatment with anti-VEGF – key model weakness.
    - ↳ Unknown if timing and proportion of people having subsequent treatments is the same for FAC and DEX.
        - Considerations of sunk cost for 36-month vs 6-month implants
    - ↳If timing and proportion having subsequent treatments differ, company model may require extensive revision and may not be possible to address within cost comparison.
- EAG base case: assume same rates of rescue anti-VEGF at same time (costs in each arm nets to zero).
    - Among those switching to anti-VEGF, there are no subsequent FAC or DEX administrations.
    - Used UK Medisoft and European IRISS study for inputs - 49% switch overall at 6 months, 18 months and 30 months.

Technical team:

- Treatment sequencing outside of scope and not a cost comparison. Could be addressed in guideline review.
- Limited data for if subsequent anti-VEGF drugs differ between treatment arms.
    - TA824: modelled 80% having subsequent anti-VEGF (clinical opinion) for 1 year after discontinuing DEX (one-off cost).
    - If assume same proportion have anti-VEGFs, has limited impact on incremental costs.

Abbreviations: FAC, Fluocinolone Acetonide; DEX, dexamethasone; IOP, intraocular pressure; AE, adverse events; RWE, real world evidence

Company vs EAG base case assumptions

Assumptions	Company	EAG	EAG Rationale	Impact
Time horizon	6 years	3 years	Limited data about number of FAC and DEX doses beyond 3 years	Large
Subsequent anti-VEGF treatment	Excluded	Included	RWE suggests subsequent rescue anti-VEGF treatment is used after FAC and DEX. Base case: 49% move to anti-VEGF in both arms, 1/3rd at 6 months, 18 months and 30 months.	Large
AE	Included	Excluded	Zero AE costs unrealistic but reflects that there is no good evidence for them differing by arm, or at least not to the extent modelled by the company. If accepted, contribution to net costs is zero	Small
Monitoring frequencies	FAC: 10; DEX: 14.2	FAC: 7; DEX: 9	Company: average frequency from 3 experts. • 1 expert said 2 monthly for DEX – EAG said too high and skews results. EAG expert: consistent with 1 company expert FAC (year 1: 4 monthly, 6 monthly thereafter); DEX (4 monthly throughout).	Moderate
Administration and monitoring vists	Separate	Combined where indicated	EAG clinical expert: monitoring and administration typically combined within a single visit. Unsure what proportion.	Small

Abbreviation: FAC, fluocinolone acetonide; DEX, dexamethasone; RWE, real world evidence; AE, adverse events

Company and EAG base case

Cost per eye	FAC	DEX	Net	% change
Company deterministic base case	[redacted]	£12,705	[redacted]	-
Company probabilistic base case (SE: 10%)	[redacted]	£14,575	[redacted]	-
EAG base case and preferred assumptions				
EAG base case (combined EAG01-06)	[redacted]	£4,142	[redacted]	151
EAG01: 3-year time horizon	[redacted]	£8,127	[redacted]	107
EAG02: 49% revert to anti-VEGF	[redacted]	£9,063	[redacted]	73
EAG03: AEs net out so can be ignored	[redacted]	£10,223	[redacted]	-3
EAG04: Monitoring frequency	[redacted]	£10,487	[redacted]	25
EAG05: Unit cost corrections	[redacted]	£14,301	[redacted]	-17
EAG06: Combined administration and monitoring	[redacted]	£11,296	[redacted]	10

Abbreviation: FAC, fluocinolone acetonide; DEX, dexamethasone; RWE, real world evidence; AE, adverse events; SE, standard error

Key decisions and assumptions

Key question	Possible options
1. What time horizon should be used?	• 3 years (EAG base case) • 6 years (company base case)
2. Should subsequent anti-VEGF treatments be included in the model?	• Excluded (company base case) • Included (EAG base case)
a) If so, should timing and proportion in FAC and DEX arms be assumed equal?	• Yes (EAG base case) • No
b) If no, is there enough data available to populate a cost-utility analysis?	• Yes – STA • No
3. Should AE be assumed equal for both FAC and DEX, so be removed from the model?	• No (company base case) • Yes (EAG base case)
4. Which monitoring frequencies are most appropriate?	• Company experts average (company base case) • EAG expert (EAG base case)
5. Should administrations be combined with monitoring visits where indicated?	• No (company base case) • Yes (EAG base case)
Does FAC have similar (or lower) costs than NICE recommended treatments?	• Yes (FAC is recommended) • No

Abbreviations: FAC, fluocinolone acetonide; DEX, dexamethasone; AE, adverse events