

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Adalimumab and dexamethasone for treating
non-infectious uveitis**

1 Recommendations

1.1 Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is:

- active disease (that is, current inflammation in the eye) and
- inadequate response or intolerance to immunosuppressants and
- systemic disease or both eyes are affected (or 1 eye is affected if the second eye has poor visual acuity) and
- worsening vision with a high risk of blindness (for example, risk of blindness that is similar to that seen in people with macular oedema).

1.2 Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following:

- new active inflammatory chorioretinal or inflammatory retinal vascular lesions, or both or
- a 2-step increase in vitreous haze or anterior chamber cell grade or
- worsening of best corrected visual acuity by 3 or more lines or 15 letters.

1.3 Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:

- active disease (that is, current inflammation in the eye) and

- worsening vision with a risk of blindness.

1.4 These recommendations are not intended to affect treatment with adalimumab and dexamethasone that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

2 Technologies

<p>Description of the technologies</p>	<p>Adalimumab (Humira, AbbVie) is a monoclonal antibody that reduces inflammation by inhibiting pro-inflammatory cytokine tumour necrosis factor-alpha.</p> <p>Dexamethasone intravitreal implant (Ozurdex, Allergan) is a biodegradable corticosteroid implant that suppresses inflammation by inhibiting the expression of pro-inflammatory mediators.</p>
<p>Marketing authorisations</p>	<p>Adalimumab is indicated ‘for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid sparing, or in whom corticosteroid treatment is inappropriate.’</p> <p>Dexamethasone intravitreal implant is indicated ‘for the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis.’</p>
<p>Adverse reactions</p>	<p>The most commonly reported adverse reactions with adalimumab are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache and musculoskeletal pain.</p> <p>The most commonly reported adverse events after treatment with dexamethasone intravitreal implant are those often seen with ophthalmic steroid treatment or intravitreal injections (elevated intraocular pressure, cataract formation and conjunctival, or vitreal haemorrhage respectively).</p> <p>For full details of adverse reactions and contraindications for adalimumab and dexamethasone, see the summaries of product characteristics.</p>

<p>Recommended doses and schedules</p>	<p>The recommended dose of adalimumab for adults with non-infectious uveitis is an initial dose of 80 mg, followed by 40 mg every other week starting 1 week after the initial dose. Adalimumab is given by subcutaneous injection. There is limited experience in starting treatment with adalimumab alone. Treatment with adalimumab can be started in combination with corticosteroids or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered off according to clinical practice from 2 weeks after starting treatment.</p> <p>The recommended dose of dexamethasone intravitreal implant is 1 implant, containing 700 micrograms of dexamethasone, to be administered intravitreally to the affected eye. Administration to both eyes concurrently is not recommended. Repeat doses should be considered when a patient experiences a response to treatment followed subsequently by a loss in visual acuity and in the clinician’s opinion may benefit from retreatment without being exposed to significant risk.</p>
<p>Prices</p>	<p>Adalimumab costs £704.28 for 2 pre-filled injections and each dexamethasone intravitreal implant costs £870.00 (excluding VAT; ‘British National Formulary’ [BNF] edition 72). Costs may vary in different settings because of negotiated procurement discounts.</p>

3 Evidence

The appraisal committee ([section 7](#)) considered evidence submitted by AbbVie and Allergan and a review of these submissions by the assessment group. See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of adalimumab and dexamethasone intravitreal implant. It considered evidence on the nature of non-infectious uveitis and the value placed on the benefits of adalimumab and dexamethasone by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need and management of non-infectious uveitis

- 4.1 The committee heard from the clinical experts that uveitis describes a group of conditions characterised by inflammation inside the eye. It understood that this appraisal covers most sight-threatening forms of non-infectious uveitis (that is, those affecting the posterior structure of eye). This includes panuveitis, as well as intermediate and posterior uveitis. The committee heard from the patient experts that symptoms include blurred vision and floaters in the eye, and sometimes pain and redness. It also heard that the condition may lead to complications such as cystoid macular oedema, vitreous haze, cataracts, glaucoma and irreversible retinal damage. People may also have sudden and temporary or progressive and permanent visual impairment. The patient experts explained that losing visual function can affect a person's ability to do daily activities, work or study. One patient expert described the psychological effect of visual impairment after going blind in 1 eye within 3 months of the condition starting, stating that knowing how quickly sight could be completely lost was very distressing. The patient experts also explained that it is common for people with uveitis to suffer depression and anxiety and to feel isolated. The clinical and patient experts advised that current treatment options are associated with significant side effects (see section 4.3). The committee concluded that uveitis has a substantial effect on quality of life.
- 4.2 The committee heard from the clinical experts that there are 3 main indications in clinical practice for treating non-infectious uveitis: vitreous haze, macular oedema and worsening vision. The committee also heard from the clinical experts and the assessment group that there is no nationally agreed pathway for treating non-infectious uveitis. The assessment group advised that in clinical practice, systemic steroids are usually used as a first-line treatment and immunosuppressants, such as mycophenolate mofetil, are either used alone or with steroids as second-line treatment. This general treatment pathway was agreed by the clinical

experts, although it was noted that treatment in clinical practice depends on whether disease is:

- active (that is, current inflammation in the eye) or inactive (that is, limited inflammation, usually because of treatment with corticosteroids or immunosuppressants; see section 4.5)
- systemic (when disease is not only in the eye) or non-systemic (when disease is limited to the eye)
- unilateral (when 1 eye is affected) or bilateral (when both eyes are affected).

It heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, but dexamethasone is generally used in people with unilateral disease. The committee concluded that the treatment pathway reflected current practice.

- 4.3 The clinical and patient experts stated that treatment options are currently restricted and there was a significant unmet need for both adalimumab and dexamethasone intravitreal implant. The committee heard from the clinical and patient experts that adalimumab and dexamethasone allow corticosteroid sparing, which is important not just for patients' short-term quality of life but also to avoid glaucoma, diabetes, stroke and heart attack. The committee recognised that patients and their carers would greatly value a new treatment which prevented or delayed sight loss, particularly if it reduced the significant side effects associated with current treatments.

Clinical effectiveness

Clinical evidence

- 4.4 The committee was aware that the comparators in the appraisal scope included corticosteroid injections and implants, systemic immunosuppressive therapies, tumour necrosis factor-alpha inhibitors (such as infliximab), intravitreal methotrexate and best supportive care.

The scope also stated that the interventions should be compared with each other. However, direct clinical evidence was only available for the interventions compared with either placebo or a sham procedure. The evidence for adalimumab came from the VISUAL I and VISUAL II trials and the evidence for dexamethasone intravitreal implant came from the HURON trial. The VISUAL trials compared adalimumab plus background therapy (that is, initial steroids tapered to zero with or without 1 immunosuppressant) with placebo plus background therapy. The HURON trial compared dexamethasone plus background therapy with a sham procedure plus background therapy. The committee noted that there was no clinical evidence which directly compared adalimumab with dexamethasone and the assessment group did not do an indirect comparison using HURON and the VISUAL trials. The assessment group advised that an indirect comparison was not appropriate because patient characteristics in VISUAL I, VISUAL II and HURON differed and there was a lack of common comparators and outcomes. Furthermore, adalimumab and dexamethasone could be used at different points in the treatment pathway. The committee agreed that there was a lack of relevant evidence on therapy for non-infectious uveitis, with varied and often limited current treatments available. However, the available clinical evidence was adequate for decision-making.

Patients included in the trials

4.5 Although the marketing authorisations for adalimumab and dexamethasone did not distinguish between active and inactive disease, the committee understood that VISUAL I and HURON included patients with active disease but VISUAL II included patients with inactive disease. The committee heard from the clinical experts that the distinction between active and inactive disease was clinically relevant because they were different populations, which would have different treatments. It heard that because maintenance treatment with immunosuppressants and corticosteroids may control inactive disease, the next line of treatment, such as adalimumab or dexamethasone intravitreal implant may not be

needed. The committee concluded that it would take these different populations into account when making its final recommendations.

- 4.6 The committee noted that the inclusion criteria for the VISUAL trials did not specify patients with macular oedema. It heard from clinical experts that people with macular oedema have a high risk of blindness. Because patients with macular oedema were not specifically included in the VISUAL trials, the clinical effectiveness of adalimumab may be underestimated in this group. It also heard from clinical experts that people with bilateral disease or systemic disease are likely to have a higher risk of blindness compared with people with unilateral or localised disease. The committee noted that most patients (over 90%) in the VISUAL trials had bilateral or systemic non-infectious uveitis. It also noted that the proportion of people with bilateral uveitis in HURON was unclear but patients had only 1 dexamethasone implant, and current clinical practice preferred dexamethasone for unilateral disease. The committee concluded that it would be useful to distinguish unilateral from systemic and bilateral disease and that people with a higher risk of blindness formed a clinically important subgroup.

Clinical-effectiveness results

- 4.7 The committee noted that the primary outcome in the VISUAL trials was a composite measure of time to treatment failure. The committee understood that the VISUAL trials showed that adalimumab had improved outcomes, such as time to treatment failure and visual acuity, compared with placebo (see table 1). The committee noted that the primary outcome in the HURON trial was the proportion of people with a vitreous haze score of 0. It understood that HURON showed that dexamethasone had improved outcomes, such as vitreous haze score and visual acuity (in the affected eye), compared with the sham procedure (see table 1). The committee concluded that there is evidence to show that both adalimumab and dexamethasone are clinically effective treatments for improving visual acuity, anterior chamber cell grade and vitreous haze.

Table 1 Summary of clinical-effectiveness results

Adalimumab versus placebo		Dexamethasone versus sham
VISUAL I	VISUAL II	HURON
Time to treatment failure (worsening of AC, VH, BCVA or new lesions)		
HR 0.50 (95% CI 0.36 to 0.70)	HR 0.57 (95% CI 0.39 to 0.84)	Not reported
Visual acuity (BCVA, logMAR, change)		
MD -0.07 (95% CI -0.11 to -0.02) [†]	MD -0.04 (95% CI -0.08 to 0.01) [‡]	MD not reported (p=0.002) at 26 weeks
Vitreous haze grade = 0		
Not reported	Not reported	RR 4.0 (95% CI 2.0 to 7.6) at 8 weeks
Not reported	Not reported	RR 2.2 (95% CI 1.1 to 4.1) at 26 weeks
Abbreviations: AC, anterior chamber; BCVA, best corrected visual acuity; CI, confidence interval; HR, hazard ratio; logMAR, logarithm of the Minimum Angle of Resolution; MD, mean difference; RR, relative risk; VH, vitreous haze. [†] Change from best state reached before week 6 to final or early termination, [‡] From baseline to final or early termination.		

Cost effectiveness

Model structure

- 4.8 The committee noted the assessment group had developed a Markov model with 4 health states in the base case (on treatment, treatment failure, permanent blindness and death). The assessment group gave 3 separate base cases, based on the underpinning trial evidence: adalimumab for active disease, adalimumab for inactive disease, and dexamethasone intravitreal implant for active disease. The assessment group noted it had not been possible to distinguish between unilateral and bilateral disease in the model; however, over 90% of patients in the VISUAL trials on adalimumab had bilateral disease. The committee concluded that the assessment group’s decision to separate its analyses into 3 separate base cases was appropriate and supported by clinical evidence and that it would need to consider all 3 base-case analyses when making its recommendations.
- 4.9 The committee was aware that the assessment group did an exploratory analysis with a ‘remission’ health state for the adalimumab model only.

This was based on clinical advice that some people who have treatment with adalimumab will have disease which is in remission (the assessment group excluded this health state from its base case because of a lack of evidence). The committee understood that the exploratory analysis assumed that after around 2 years of stable disease, treatment is no longer needed. This is because the disease is in remission but patients will have the same health-related quality of life as when they were having treatment. The committee heard from the clinical experts that the disease could be expected to go into remission in at least some of the people who have adalimumab. The committee concluded that although there is no evidence for remission, it was reasonable to assume that at least some people's disease could be in remission after treatment with adalimumab.

Modelling the rate of blindness

- 4.10 The committee noted that the follow-up time in the HURON trial was 26 weeks, but a maximum follow-up of 80 weeks was included in the VISUAL trials. None of the trials reported patients with permanent legal blindness. The assessment group advised that the rate of blindness and the relative risk of blindness associated with adalimumab and dexamethasone had a large effect on the incremental cost-effectiveness ratio (ICER) and did scenario analyses to model this potential effect. The committee acknowledged there was a lack of robust, long-term studies for the rate of blindness but concluded that the scenario analyses including blindness were appropriate for decision-making because it is likely that both adalimumab and dexamethasone had an effect on the rate of blindness, although the extent of this effect was uncertain.
- 4.11 The committee understood that in its base case, the assessment group preferred to use a constant annual rate of blindness of 0.0066 from Dick et al. (2016), a retrospective analysis of 1,769 insurance claims of adults with non-infectious intermediate uveitis, posterior uveitis or panuveitis in the US. In contrast, the company for adalimumab preferred the higher rate of blindness (0.0374) that was used in a scenario analysis by the

assessment group. This rate was reported in a retrospective review of 315 medical records in the UK (Durrani et al. 2004). However, the assessment group advised that this study included a wider population compared with the scope of this appraisal (only 61% of patients had posterior, intermediate or panuveitis and age ranged from 7 to 86 years) and was done in a tertiary centre in which patients are more likely to have severe, and often bilateral uveitis. The committee was aware that a higher rate of blindness would lead to more favourable cost-effectiveness results for the interventions. The committee agreed that for people at higher risk of blindness (for example, people with macular oedema and bilateral disease) the background rate of blindness is likely to be higher than in the base case. However, it noted that macular oedema was not the only precursor to blindness. The committee also agreed that the risk of permanent legal blindness in people having dexamethasone was probably lower compared with the risk of blindness in people having adalimumab. This is because dexamethasone is often used to treat unilateral disease while adalimumab is often used to treat bilateral disease later in the treatment pathway. The committee concluded that the rate of blindness in people at high risk was uncertain but likely to be higher than in the base case (0.0066). The committee also concluded the base-case rate of 0.0066 was acceptable for unilateral disease, because although this group might include people with macular oedema and at a higher risk of unilateral blindness, this was not the same as permanent legal blindness.

- 4.12 The committee noted that the assessment group's base case used a relative risk of blindness of 0.5 for dexamethasone (that is, a 50% lower rate of blindness in the dexamethasone group compared with the comparator group). For adalimumab, the base case did not allow blindness in either the adalimumab or comparator arms while on treatment, and used the same overall rate of blindness after treatment failure, which was strictly defined in the VISUAL trials. However, there was a lack of evidence to support a relative risk of 0.5 for dexamethasone. The clinical experts agreed that there was a lack of evidence to support

this assumption, but considered a value of 0.5 clinically plausible for the affected eye. For adalimumab, the committee accepted the base-case assumptions. The committee concluded that the assessment group's approach to modelling was appropriate for decision-making provided that the dexamethasone rate is only applied to the affected eye, unless both eyes were affected and treated.

- 4.13 The committee noted that the assessment group did additional scenario analyses for adalimumab for active non-infectious uveitis using the committee's preferred utility for blindness of 0.57. The scenarios combined varying the relative risk of blindness with treatment and the rate at which treatment is stopped because of remission. The committee recalled its earlier conclusion that at least some people having adalimumab are likely to go into remission (see section 4.9). The committee concluded that these scenarios were appropriate for decision-making because they accounted for both the possible effect on blindness and the additional benefit of remission.

Health-related quality of life

- 4.14 The committee was aware that the quality-of-life data from the clinical trials were assumed to include the effects of adverse events during the treatment period. Utility values for blindness were also taken from the literature. The committee heard from the patient and clinical experts that they were unsure whether this approach to modelling utility included the effect of uveitis on the whole person. This was because uveitis substantially affected quality of life, with visual disability having significant consequences for people (including depression and stress, for example, because of a loss of ability to support self and family), and their families and carers. However, the assessment group stated that the trial included holistic treatment benefit, as well as the main costs of adverse events and blindness. The committee agreed that uveitis had a significant effect on quality of life, and that there were limited data to inform the utility assumptions. However, it was aware that the utility values are designed to

represent whole person health. The committee concluded that the utility values used were appropriate for decision-making.

- 4.15 The committee considered the approach to modelling the utility of the blindness health state. The committee noted that the quality-of-life value used in the base case (0.38 from Czoski-Murray et al. 2009) was low, and agreed that scenario analyses using the higher utility of 0.57 (from Brown et al. 1999) were more plausible. It was aware that in the model people were either permanently legally blind or not blind. The committee was aware this omitted the effect of worsening visual acuity and that level of vision was likely to be a continuous variable. The committee further discussed the effect of blindness depending on whether disease was unilateral or bilateral, which was not captured in the model. In its experience of previous appraisals for eye diseases, the utility loss of blindness in both eyes was likely to be much higher than in unilateral blindness.
- 4.16 The committee noted that EQ-5D data were reported at baseline and follow-up in the VISUAL trials, but only at baseline in HURON. It was aware that all 3 trials also assessed health-related quality of life using the Visual-Functioning Questionnaire (VFQ-25) and that this measure is more specific to visual function. The committee understood that to model utilities for adalimumab over time, the assessment group used EQ-5D data directly from the VISUAL trials. To estimate utility over time for dexamethasone, the assessment group used individual patient-level VFQ-25 data and mapped these to EQ-5D using a regression analysis. Individual patient-level data for adalimumab were not made available in time for the assessment group to use them. The committee heard from the assessment group that using VFQ-25 data instead of EQ-5D data had only a small effect on the ICERs. The committee concluded that the methodology used to derive this utility was acceptable for decision-making.

Resource use

- 4.17 The committee noted that to calculate the cost of blindness, the assessment group assumed that 30% of patients would have residential care. It understood that this cost was based on a [health technology assessment](#) (Colquitt et al. 2008) on treating age-related macular degeneration, which is likely to affect people who are older than those with uveitis. It recalled that people with non-infectious uveitis are between 20 to 50 years and only a small proportion would need residential care. The committee concluded that the proportion of people needing residential care is likely to be overestimated in the assessment group's model and, if this proportion were smaller, the ICERs would increase (that is, the treatments would become less cost effective) for the scenario analyses involving blindness.
- 4.18 The committee heard from the clinical experts that using multiple dexamethasone implants consecutively was associated with adverse events, including increased intraocular pressure and cataracts. It heard that for this reason, the clinical experts would use a maximum of 3 implants consecutively although this may vary in clinical practice. It also heard from the assessment group that using multiple implants consecutively was likely to produce similar cost-effectiveness results because the model assumed that dexamethasone would only provide a treatment benefit for around 6 months. The committee concluded that consecutive use of dexamethasone was unlikely to have a large effect on the cost-effectiveness analyses.

Most plausible incremental cost-effectiveness ratios

- 4.19 The committee recalled its earlier concern that the cost of blindness had been overestimated in the model (see section 4.17). This meant that the base-case and scenario analyses for both interventions favoured the interventions that were more effective in reducing blindness. However, it also noted that there was uncertainty around the background rate of blindness (see sections 4.10 and 4.11), which it considered had been

underestimated for the high-risk groups for whom treatment with adalimumab or dexamethasone is possible. This was likely to make the cost-effectiveness results more conservative. The committee concluded that, although there was uncertainty, the reduction (that is, improvement) in ICERs resulting from overestimated costs of blindness were likely to be offset by the low rate of background blindness in this high-risk group.

4.20 The committee noted that the assessment group's base-case ICER for adalimumab in patients with inactive non-infectious uveitis was £321,405 per quality-adjusted life year (QALY) gained. It noted that all the ICERs in all the scenario analyses were above £80,000 per QALY gained. The committee agreed that these ICERs were substantially above the range normally considered a cost-effective use of NHS resources. The committee also noted that people with inactive disease would be unlikely to have treatment with adalimumab in clinical practice (see section 4.5). Therefore the committee did not recommend adalimumab for treating inactive non-infectious uveitis.

4.21 The committee noted that the assessment group's base-case ICER for adalimumab in patients with active non-infectious uveitis was £95,506 per QALY gained. However, this base case did not take account of its reasoning that there would be a relatively severely affected subgroup of patients (see section 4.6). The committee noted that disease was likely to be more severe in people with bilateral disease later in the treatment pathway. It agreed that the treatment would be more cost effective in those at higher risk of permanent legal blindness, and bilateral disease with macular oedema was a useful proxy for this. However, the committee also recognised that people with unilateral disease in the better seeing eye were also at a high risk of permanent blindness if they have poor visual acuity in the other eye. Using its preferred assumptions for severe disease (see section 4.6), high rates of blindness (see sections 4.11 and 4.12), utility values (see section 4.15) and occasional remission (see section 4.9), adalimumab resulted in ICERs that ranged from £23,688 to £37,279 per QALY gained, and these were probably lower because the

rate of blindness was likely to have been underestimated for patients with progressive loss of visual acuity (see section 4.11). The committee also took into account the lack of available treatment options for this subgroup, the evidence from the patient and clinical experts about the adverse effects associated with current treatment options and comments from consultation. Taking all of this into account, it recommended adalimumab as a cost-effective use of NHS resources for treating non-infectious uveitis in the posterior segment of the eye in adults, if there is:

- active disease and
- an inadequate response or intolerance to immunosuppressants and
- systemic disease or both eyes are affected (or 1 eye is affected if the second eye has poor visual acuity) and
- worsening vision with a high risk of blindness (for example, risk of blindness that is similar to that seen in people with macular oedema).

The committee also agreed that a stopping rule should be included, which reflected the strict criteria for defining treatment failure in the VISUAL I trial. Based on these criteria, it concluded that treatment should be stopped if there is evidence of 1 of the following:

- new active inflammatory chorioretinal or inflammatory retinal vascular lesions or both or
- a 2-step increase in vitreous haze or anterior chamber cell grade or
- worsening of best corrected visual acuity by 3 or more lines or 15 letters.

The committee's recommendations are therefore in line with the clinical trial evidence that has underpinned the marketing authorisation granted by the regulator.

4.22 The committee noted that the assessment group's base-case ICER for dexamethasone in patients with active uveitis was £20,058 per QALY gained. The committee recalled that the clinical experts stated that people who have dexamethasone in current clinical practice are likely to have

disease affecting only 1 eye (see section 4.2), but the proportion of unilateral uveitis in the HURON trial was unclear (see section 4.6). Using the committee’s preferred assumptions for unilateral disease (see section 4.6), low rates of blindness (see section 4.11 and section 4.12) and utility values (see section 4.15) resulted in ICERs that ranged between £25,000 and £49,000 per QALY gained. The committee considered that the lower ICER would apply to patients whose better seeing eye needed treatment, because this reflected a risk of bilateral blindness; the higher ICER applied to patients at no risk of bilateral blindness, and was likely to be a significant overestimate because the disutility of monocular blindness was not modelled. The committee decided that dexamethasone for monocular disease with worsening vision and a risk of blindness was an acceptable use of NHS resources and that patient need is high. The committee concluded that the ICER for unilateral disease with a risk of blindness was likely to be in the range normally considered cost effective, and recommended dexamethasone for treating active non-infectious uveitis with worsening vision and a risk of blindness.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title: Adalimumab and dexamethasone for treating non-infectious uveitis	Section
Key conclusion		
Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids, only if there is: <ul style="list-style-type: none"> • active disease (that is, current inflammation in the eye) and • inadequate response or intolerance to immunosuppressants and • systemic disease or both eyes are affected (or 1 eye is affected if the second eye has poor visual acuity) and 		1.1 to 1.3, 4.19 to 4.22

- worsening vision with a high risk of blindness (for example, risk of blindness that is similar to that seen in people with macular oedema).

Stop adalimumab for non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids if there is 1 of the following:

- new active inflammatory chorioretinal, inflammatory retinal vascular lesions or both or
- a 2-step increase in vitreous haze or anterior chamber cell grade or
- worsening of best corrected visual acuity by 3 or more lines or 15 letters.

Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:

- active disease (that is, current inflammation in the eye) and
- worsening vision with a risk of blindness.

The committee concluded that there is evidence to show that both adalimumab and dexamethasone are clinically effective treatments because there were significant improvements in the primary outcomes for the VISUAL trials (time to treatment failure: hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.36 to 0.70 in VISUAL I; and HR 0.57, 95% CI 0.39 to 0.84 in VISUAL II), and HURON (vitreous haze score relative risk [RR] 4.0, 95% CI 2.0 to 7.6 at 8 weeks; and RR 2.2, 95% CI 1.1 to 4.1 at 26 weeks).

For adalimumab in patients with active non-infectious uveitis, the committee considered incremental cost-effectiveness ratios (ICERs) ranged from £23,688 to £37,279 per quality-adjusted life year (QALY) gained as most plausible and noted that they were

<p>probably lower because the rate of blindness was likely to have been underestimated for patients with progressive loss of visual acuity.</p> <p>For adalimumab in patients with inactive non-infectious uveitis, the committee noted that all the ICERs in all the scenario analyses were above £80,000 per QALY gained, which is above the range normally considered a cost-effective use of NHS resources.</p> <p>The committee considered that the most plausible ICER for dexamethasone was between £25,000 and £49,000 per QALY gained. It noted that the lower ICER would apply to patients whose better seeing eye needed treatment, because this reflected a risk of bilateral blindness; the higher ICER applied to patients at no risk of bilateral blindness, and was likely to be a significant overestimate because the disutility of monocular blindness was not modelled. The committee concluded that the ICER was likely to be in the range normally considered cost effective.</p>		
Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The committee heard from patient experts that symptoms include blurred vision and floaters in the eye, and sometimes pain and redness. It also heard that the condition may lead to complications such as cystoid macular oedema, vitreous haze, cataracts, glaucoma and irreversible retinal damage. The committee concluded that uveitis had a great effect on quality of life.</p>	<p>4.1</p>
The technologies		

<p>Proposed benefits of the technologies</p> <p>How innovative is the technology/are the technologies in its/their potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee recognised that patients and their carers would greatly value a new treatment which prevented or delayed sight loss, particularly if it reduced the significant adverse events associated with current treatments.</p>	<p>4.3</p>
<p>What is the position of the treatment(s) in the pathway of care for the condition?</p>	<p>The committee heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, but dexamethasone is generally used in people with unilateral disease.</p>	<p>4.2</p>
<p>Adverse reactions</p>	<p>The most commonly reported adverse reactions with adalimumab are infections, injection site reactions, headache and musculoskeletal pain. The most commonly reported adverse events after treatment with dexamethasone intravitreal implant are those often seen with ophthalmic steroid treatment or intravitreal injections.</p>	<p>2</p>
<p>Evidence for clinical effectiveness</p>		
<p>Availability, nature and quality of evidence</p>	<p>The committee was aware that the clinical evidence came from 3 trials: VISUAL I and VISUAL II (adalimumab) and HURON (dexamethasone intravitreal implant). The VISUAL trials compared adalimumab plus</p>	<p>4.4</p>

	background therapy (that is, initial steroids tapered to zero with or without 1 immunosuppressant) with placebo plus background therapy. The HURON trial compared dexamethasone plus background therapy with a sham procedure plus background therapy. The committee noted that there was no clinical evidence which directly compared adalimumab with dexamethasone and the assessment group did not do an indirect comparison using HURON and the VISUAL trials.	
Relevance to general clinical practice in the NHS	The committee concluded the 3 trials were relevant for this appraisal.	4.4
Uncertainties generated by the evidence	The committee concluded that there was a lack of relevant evidence on therapy for non-infectious uveitis, with varied and often limited current treatments available. However, the available clinical evidence was adequate for decision-making.	4.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that it would be useful to distinguish unilateral from systemic and bilateral disease and that people with a higher risk of blindness formed a clinically important subgroup.	4.6

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The committee understood that the VISUAL trials showed that adalimumab had improved outcomes, such as time to treatment failure (HR 0.50, 95% CI 0.36 to 0.70 in VISUAL I and HR 0.57, 95% CI 0.39 to 0.84 in VISUAL II) and visual acuity, compared with placebo. It also understood that HURON showed that dexamethasone had improved outcomes, such as vitreous haze score (RR 4.0, 95% CI 2.0 to 7.6 at 8 weeks and RR 2.2, 95% CI 1.1 to 4.1 at 26 weeks) and visual acuity (in the affected eye), compared with the sham procedure.</p>	<p>4.7</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The committee noted the assessment group had developed a Markov model with 4 health states in the base case (on treatment, treatment failure, permanent blindness, and death). The assessment group gave 3 separate base cases, based on the underpinning trial evidence: adalimumab for active disease, adalimumab for inactive disease, and dexamethasone intravitreal implant for active disease.</p>	<p>4.8</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>For both adalimumab and dexamethasone, the committee acknowledged a lack of evidence but concluded that:</p> <ul style="list-style-type: none"> • treatment is likely to have an effect on the future rate of blindness, although the extent of this effect was uncertain • the utility loss of blindness in both eyes was likely to be much higher than in unilateral blindness. <p>For adalimumab, the committee concluded that scenarios accounting for both the potential effect of blindness and the additional benefit of remission were most appropriate for decision-making and it was reasonable to assume that at least some people’s disease would be in remission after treatment.</p>	<p>4.9, 4.10, 4.15, 4.19</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee noted that the disutility of monocular blindness was not modelled.</p> <p>The committee further discussed the effect of blindness depending on whether disease was unilateral or bilateral, which was not captured in the model. In its experience of previous appraisals for eye diseases, the utility loss of blindness in both eyes was likely to be much higher than in unilateral blindness.</p>	<p>4.15</p>
<p>Are there specific groups of people for whom the technologies are particularly cost effective?</p>	<p>The committee agreed that treatment with adalimumab and dexamethasone vitreal implant would be more cost effective in those at higher risk of permanent legal blindness, and it agreed that the presence of bilateral disease with macular oedema was a useful proxy for this. However, it noted that macular oedema was not the only precursor to blindness. The committee also recognised that people with unilateral disease in the better seeing eye were also at a high risk of permanent blindness if they had poor visual acuity in the other eye.</p>	<p>4.11, 4.19 to 4.22</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee understood that the rate and relative risk of blindness were key drivers of the cost effectiveness.</p>	<p>4.10</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>For adalimumab in patients with active disease, the committee considered ICERs that ranged from £23,688 to £37,279 per QALY gained as most plausible and noted they were probably lower because the rate of blindness was likely to have been underestimated for patients with progressive loss of visual acuity.</p> <p>For adalimumab in patients with inactive uveitis, the committee noted that all the ICERs in all the scenario analyses were above £80,000 per QALY gained.</p> <p>The committee considered that the most plausible ICER for dexamethasone was between £25,000 and £49,000 per QALY gained. It noted that the lower ICER would apply to patients whose better seeing eye needed treatment, because this reflected a risk of bilateral blindness.</p>	<p>4.19 to 4.22</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>Not applicable</p>	
<p>End-of-life considerations</p>	<p>Not applicable</p>	
<p>Equalities considerations and social value judgements</p>	<p>The committee did not identify any specific equalities' considerations</p>	

5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has non-infectious uveitis in the posterior segment of the eye and the doctor responsible for their care thinks that dexamethasone or adalimumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Stevens

Chair, appraisal committee

June 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Marcela Haasova and Abitha Senthinathan

Technical leads

Carl Prescott and Alexandra Filby

Technical advisers

Stephanie Yates

Project manager

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