NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Adalimumab and dexamethasone for treating non-infectious uveitis

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using adalimumab and dexamethasone in the NHS in England. The appraisal committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using adalimumab and dexamethasone in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 4 April 2017

Second appraisal committee meeting: 12 April 2017

Details of membership of the appraisal committee are given in section 7.

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
- macular oedema
- inadequate response to immunosuppressants
- systemic disease or both eyes are affected and
- worsening vision with a risk of blindness.

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
- anterior chamber cell grade of 0.5+ or less
- vitreous haze grade of 0.5+ or less
- 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
- macular oedema.

1.4 This guidance is not intended to affect the position of patients whose treatment with adalimumab or dexamethasone was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place

for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 Technologies

Description of the technologies	Adalimumab (Humira, AbbVie) is a monoclonal antibody that reduces inflammation by inhibiting proinflammatory cytokine tumour necrosis factor-alpha. Dexamethasone intravitreal implant (Ozurdex, Allergan) is a biodegradable corticosteroid implant that suppresses inflammation by inhibiting the expression of pro-inflammatory mediators.
Marketing authorisations	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.' 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.'
Adverse reactions	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. 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). For full details of adverse reactions and contraindications for adalimumab and dexamethasone, see the summaries of product characteristics.

Recommended doses and schedules	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. 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 physician's opinion may benefit from retreatment without being exposed to significant risk.
Prices	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.

3 Evidence

The appraisal committee (section 7) considered evidence from a number of sources. 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, having 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) and 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 carry out daily living 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 substantial adverse events (see section 2 and section 4.3). The committee concluded that uveitis had 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 (AG) that there is no nationally agreed pathway for treating non-infectious uveitis. The AG 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 in combination 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, whereas dexamethasone is used in people with unilateral disease. The committee concluded that the general 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 their 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 adverse events 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, immunosuppressants with or without steroids) with placebo plus background therapy and HURON 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 AG did not carry out an indirect comparison using HURON and the VISUAL trials. The AG 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. The committee agreed that there was a lack of 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 whereas 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 and

because this group was not specifically included in the VISUAL trials, the clinical effectiveness of adalimumab may be underestimated for people with macular oedema. 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 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. 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. 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.

Cost effectiveness

Model structure

4.8 The committee noted the AG had developed a Markov model with 4 health states in the base case (on treatment, treatment failure, permanent blindness, and death). The AG had presented 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 AG 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 AG's decision to separate its analyses into 3 separate base cases was appropriate and supported by clinical evidence, and that it would need to make 3 separate recommendations when making its final decisions.

4.9 The committee was aware that the AG carried out 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 AG 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 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, whereas a maximum follow-up of 80 weeks was included in the VISUAL trials. None of the trials reported patients with permanent legal blindness. The AG 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 carried out 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 AG 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 AG. This rate was reported in a retrospective review of 315 medical records in the UK (Durrani et al. 2004). However, the AG 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 carried out 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. 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 legal blindness.

4.12 The committee noted that the AG'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 plausible for the affected eye. The committee concluded that the AG'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.

Health-related quality of life

4.13 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 AG 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.

4.14 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 Browne et al 2012) 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.

4.15 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 AG advised that EQ-5D data were more likely to capture wider factors that may affect health-related quality of life. The committee understood that to model utilities for adalimumab over time, the AG used EQ-5D data directly from the VISUAL trials. To estimate utility over time for dexamethasone, the AG 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 AG to use them. The committee heard from the AG 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

4.16 The committee noted that to calculate the cost of blindness, the AG 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 AG's model and this would increase the ICERs (that is, the treatments would become less cost effective) for the scenario analyses involving blindness.

4.17 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, a maximum of 3 implants would be used consecutively in clinical practice. It also heard from the AG 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.

Exploratory analyses with blindness and remission for adalimumab

4.18 The committee noted that the AG carried out additional scenario analyses for adalimumab for active non-infectious uveitis. 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 most appropriate for decision-making because they accounted for both the possible effect on blindness and the additional benefit of remission.

Most plausible incremental cost-effectiveness ratios

4.19 The committee noted that the AG'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. 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, because its mechanism of action suggests limited benefit (see section 4.5). Therefore it concluded that adalimumab could not be recommended for treating inactive non-infectious uveitis.

4.20 The committee noted that the AG'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. Using its preferred assumptions for severe disease (see section 4.6), blindness (see section 4.11 and section 4.12) and occasional remission (see section 4.18), adalimumab resulted in ICERs that were around £33,000 per QALY gained, and that 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 4.10). The committee also took into account the lack of available treatment options for this subgroup, and the evidence from the patient and clinical experts about the adverse effects associated with current treatment options. Taking all of this into account, itrecommended 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
- macular oedema
- an inadequate response to corticosteroids or immunosuppressants
- systemic disease or both eyes are affected and
- worsening vision with a risk of blindness.

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
- anterior chamber cell grade of 0.5+ or less
- vitreous haze grade of 0.5+ or less
- worsening of best corrected visual acuity by 3 or more lines or 15 letters.

4.21 The committee noted that the AG'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) and blindness (see section 4.11 and section 4.12) 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 real risk of 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. This would bring the ICER for unilateral disease with a higher risk of blindness closer to the acceptable range. The committee decided that dexamethasone for monocular disease with macular oedema was still an acceptable use of NHS resources because:

- the drug is already available for other causes of macular oedema
- it is relatively inexpensive (£870 per implant, and the total costs were £580 more expensive than the comparator in the base case) and

- patient need is high (see section 4.1).

Taking all of this into account, the committee concluded that the ICER was likely to be within the range normally considered cost-effective, and recommended dexamethasone for treating active non-infectious uveitis with macula oedema.

4.22 The committee recalled its earlier concern that the cost of blindness had been overestimated in the model (see section 4.16). 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 the background rate of blindness had probably been underestimated for the high-risk groups for whom treatment with adalimumab or dexamethasone is recommended in this guidance, which was likely to make the cost-effectiveness results more conservative. The committee concluded that although there was uncertainty about the effect of this, the reduction (that is, improvement) in ICERs resulting from overestimated costs of blindness were likely to be at least partly offset by the low rate of background blindness in this high-risk group.

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: • active disease, that is, current inflammation in the eye • macular oedema • inadequate response to immunosuppressants.		1.1**Error! Reference source not found.** to 1.3

• systemic disease or both eyes are affected and • worsening vision with a risk of blindness. 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 • anterior chamber cell grade of 0.5+ or less • vitreous haze grade of 0.5+ or less • 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 • macular oedema. For adalimumab in patients with active non-infectious uveitis, the committee considered incremental cost-effectiveness ratios (ICERs) that were around £33,000 per quality-adjusted life year (QALY) gained as most plausible and noted that they were probably lower because the rate of blindness was likely to have been underestimated for patients with progressive loss of visual acuity. 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, which is above the range normally considered a cost-effective use of NHS resources.	4.19 to 4.21

The committee considered that the most plausible incremental 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 real risk of 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.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	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 substantial effect on quality of life.	4.1
The technologies		
Proposed benefits of the technologies How innovative is the technology/are the technologies in its/their potential to make a significant and substantial impact on health-related benefits?	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.	4.3

What is the position of the treatment(s) in the pathway of care for the condition?	The committee heard from clinical experts that adalimumab would generally be used in people with bilateral or systemic disease or both, whereas dexamethasone is used in people with unilateral disease.	4.2
Adverse reactions	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.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	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 background therapy (that is, immunosuppressants with or without steroids) with placebo plus background therapy and HURON 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	4.4

	did not carry out 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 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
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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. It also 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.	4.7
Evidence for cost effectiveness		

Availability and nature of evidence	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 had presented 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.	4.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	For both adalimumab and dexamethasone, the committee acknowledged a lack of evidence but concluded that: • 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. 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.	4.9, 4.10, 4.14, 4.18

Incorporation of health-related quality-of-life benefits and utility values 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?	The committee noted that the disutility of monocular blindness was not modelled. 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.	4.14
Are there specific groups of people for whom the technologies are particularly cost effective?	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.	4.19 to 4.21
What are the key drivers of cost effectiveness?	The committee understood that the rate and relative risk of blindness were key drivers of the cost effectiveness.	4.10

Most likely cost-effectiveness estimate (given as an ICER)	For adalimumab in patients with active disease, the committee considered ICERs that were around £33,000 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. 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. 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 real risk of blindness.	4.19 to 4.21
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable	
End-of-life considerations	Not applicable	
Equalities considerations and social value judgements	The committee did not identify any specific equalities' considerations.	

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 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. 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

March 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 Hassova and Abitha Senthinathan
Technical leads

Carl Prescott
Technical adviser

Stephanie Yates
Project manager

ISBN: [to be added at publication]