

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Holoclar for treating limbal stem cell deficiency
after eye burns**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ex vivo expanded autologous human corneal epithelial cells in the NHS in England. The appraisal committee has considered the evidence submitted by the company 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 this technology. 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 ex vivo expanded autologous human corneal epithelial cells 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: 8 May 2017

Second appraisal committee meeting: 16 May 2017

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

1 Recommendations

1.1 Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells) is recommended as an option in people with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity) after eye burns, only if:

- only 1 eye is treated and
- they have already had a conjunctival limbal allograft from a living, related donor and/or a conjunctival limbal autograft when 1 eye is affected, or
- they have already had a conjunctival limbal allograft when both eyes are affected and
- the company provides it with the discount agreed in the patient access scheme.

1.2 This recommendation is not intended to affect treatment with Holoclar that was started in the NHS before this guidance was published. People having treatment outside this recommendation 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 The technology

Description of the technology	Ex vivo expanded autologous human corneal epithelial cells containing stem cells (Holoclar, Chiesi Farmaceutici) is a treatment used in the eye to replace damaged cells on the corneal surface.
Marketing authorisation	It has a conditional marketing authorisation for ‘the treatment of adult patients with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity), unilateral or bilateral, due to physical or chemical ocular burns’. At least 2 mm ² of undamaged limbus is needed for biopsy before it can be used.
Adverse reactions	For full details of adverse reactions and contraindications, see the summary of product characteristics .
Recommended dose and schedule	Exact dosage depends on the size of the corneal surface: the recommended dose is 79,000 to 316,000 cells/cm ² A biopsy is first taken of the eye, which needs at least 2 mm ² of undamaged tissue. The treatment is then implanted in the eye.
Price	According to the company’s submission, a single treatment for 1 eye costs £80,000 excluding VAT. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of Holoclar, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee (section 7) considered evidence submitted by Chiesi Farmaceutici and a review of this submission by the evidence review group (ERG). 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 Holoclar (ex vivo expanded autologous human

corneal epithelial cells containing stem cells), having considered evidence on the nature of moderate to severe limbal stem cell deficiency after eye burns and the value placed on the benefits of the treatment by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Treatment pathway and unmet need

- 4.1 The committee was aware that limbal stem cell deficiency (LSCD) is caused by an injury (such as a chemical or physical burn) to the source of limbal stem cells, which interrupts the renewal and replacement of the surface of the cornea. LSCD can either be unilateral (in 1 eye) or bilateral (in both eyes). The committee heard from the clinical experts that LSCD can be life-changing: in addition to visual impairment, the condition is associated with high levels of pain and photophobia. LSCD also represents a major psychological burden, both from the trauma of the original incident and the ongoing management of eye disfigurement. The highly visible nature of the injury can also impair a person's confidence and cause social isolation. Some people with LSCD are unable to continue working because of the physical or psychological effects. The committee agreed that LSCD can be a life-changing and severely debilitating condition.
- 4.2 The committee heard from the clinical experts that the aim of treatment for LSCD is to restore the surface of the eye, achieve corneal clarity and improve visual acuity. Current practice usually starts with supportive care treatments such as lubrication, autologous serum eye drops, and therapeutic soft and scleral contact lenses. Conservative surgery such as corneal scraping may also be offered before attempting limbal stem cell transplantation. Limbal stem cell transplantation includes a number of invasive surgical options to transplant stem cells to the affected eye which differ in terms of where the cells come from and how they are transferred, specifically:

- conjunctival limbal autograft, in which stem cells are taken from the patient's healthy eye
- conjunctival limbal allograft, in which stem cells are taken from a living, related donor or dead donor
- keratolimbal allograft, in which the entire limbus may be transplanted from a dead donor, using the cornea as carrier tissue.

4.3 The committee heard from the clinical experts that successfully treating LSCD could be life-changing. However, current treatments are associated with many disadvantages. Conjunctival limbal autograft needs a relatively large amount of donor tissue from the healthy eye (equivalent to around 40% of the available reserves of the donor tissue). This increases the risk of damage to the donor eye: the clinical experts stated that 3% to 5% of patients having an autograft would have permanent serious damage. The clinical experts also estimated a transplant success rate with conjunctival limbal autograft of only 50%. Therefore, patients often choose to not have the treatment because their perceived risk of damage to the donor eye was not worth the chance of the procedure being a success in the affected eye. Indeed, 1 clinical expert stated they no longer did conjunctival limbal autografts because of these risks, although they acknowledged that the procedure is still used in clinical practice. Because both conjunctival limbal and keratolimbal allografts rely on external donors, they need immunosuppression which is in itself associated with several side effects. Even when treatment is successful, most allografts fail within 5 years. The clinical experts explained that finding a source of donor tissue can also be problematic.

4.4 The committee asked the clinical experts if patients with bilateral LSCD would have treatment in 1 or both eyes. It heard that ideally both eyes would be treated, but in practice it is likely for 1 eye to be worse than the other and that only the worst eye would be treated. The committee also asked if any of the procedures could be done more than once in the same eye. The clinical experts stated this would be unlikely for existing procedures, but that Holoclar represents a more viable option for

retreatment because it needs a smaller amount of tissue. The smaller biopsy also means a much lower risk of damage to the donor eye; 1 clinical expert stated that in data for around 1,000 Holoclar procedures, they were unaware of any instances of damage to the patient's donor eye. The clinical experts stated that there is a subgroup of patients who have had conjunctival limbal autograft previously whose only option for further treatment was Holoclar. The committee concluded that the company had used the most appropriate comparators in its submission (that is: conjunctival limbal autograft, conjunctival limbal allograft, keratolimbal allograft and best supportive care), and Holoclar offered several advantages over these treatments.

Clinical effectiveness

- 4.5 The committee noted that the evidence for Holoclar (3 studies: HLSTM01, HLSTM03 and HLSTM04) and the comparators was mostly from case series. These studies offer poorer quality evidence, because they do not contain a comparison group. The comparator evidence consisted of 23 smaller studies with high levels of heterogeneity, which the company, ERG and committee agreed made them unsuitable for data pooling. The committee noted that data were available for a reasonably high number of patients for Holoclar given the rarity of the condition (n=219 across all studies). However, the company had run statistical analyses on the available data despite case series not being designed for this purpose (they are intended to be descriptive only). The committee also noted that the clinical evidence for Holoclar was limited to treating 1 eye only (of the 13 patients with bilateral disease, only 1 had treatment in both eyes). In the absence of stronger evidence in this disease area, the committee accepted this clinical evidence for its decision-making. However, it agreed that when making its recommendations it would need to take into account that no clinical evidence had been presented for using Holoclar in more than 1 eye.

Clinical evidence results

- 4.6 The primary outcome of the pivotal HLSTM01 study was treatment success, defined as stable corneal epithelium without significant recurrence of neovascularisation 12 months after treatment. The main secondary outcomes included symptom resolution (pain, burning and photophobia), inflammation, neovascularisation, visual acuity, number of successful keratoplasties and safety.
- 4.7 The results from HLSTM01 showed that 72.1% of patients had a successful Holoclar transplant. For the comparators, transplant success varied between 60.0% and 100.0%. Given its concerns with the quality of evidence (section 4.5), the committee asked the clinical experts if these success rates were likely to be reflective of those in clinical practice. The experts stated that the results for Holoclar were plausible, but that the results for the comparators should be interpreted with more caution. They considered the studies of conjunctival limbal autograft to be poorly conducted and biased, and the rates to be overestimated (in their experience, success rates were closer to 50%). The committee concluded that the evidence showed Holoclar to be an effective treatment for several outcomes described in section 4.6. However, there was uncertainty about the comparator success rates and the relative effectiveness of Holoclar compared with them.

Cost effectiveness

Model structure

- 4.8 The company presented 2 separate models: a 'unilateral' and a 'bilateral' model. The models were similar, with both consisting of a decision tree followed by a Markov model, but the bilateral model assumed that patients had treatment in both eyes (and so included an additional year without treatment before treating the second eye). The evidence review group (ERG) considered the model to be reasonably well constructed. However, the committee noted that the company had not actually presented separate results for unilateral and bilateral populations. The 2 models did

not, in fact, distinguish between unilateral and bilateral disease; both models included exactly the same population (that is, both included patients with unilateral and bilateral disease). Instead, the main difference was that only 1 eye was treated in the unilateral model, whereas both eyes were treated in the bilateral model. The committee agreed that it would be more informative to consider the company's unilateral model as the '1-eye treatment' model and the bilateral model as the '2-eye treatment' model. The committee concluded that the model structures were acceptable for its decision-making, but that it would be difficult to distinguish between unilateral and bilateral populations when making its final recommendations on the cost-effectiveness modelling.

Discount rate

4.9 The company had deviated from the reference case by using a discount rate for future costs and benefits of 1.5%, rather than 3.5% as outlined in the [NICE guide to the methods of technology appraisal](#). The company justified this by explaining that it believed Holoclara to have a prolonged effect (over 30 years), and that it could return patients to a high utility state. The committee was aware that the NICE methods guide states that when appraising treatments that 'restore people who would otherwise die or have severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years)', non-reference case rates may be considered. However, the committee noted that it is rarely considered appropriate to change the discount rate and that LSCD was very different from the fatal and near-fatal conditions implied by the methods guide. The committee therefore concluded that the company should have used a 3.5% discount rate.

Modelled long-term success rates

4.10 The committee noted that if treatment with Holoclara were successful at 1 year, it remained successful for the lifetime of the model. When questioned about the plausibility of this assumption, the clinical experts stated that there currently was not enough evidence to support any

assumptions about the long-term effectiveness of Holoclar. However, the transplant being successful at 1 year would demonstrate that the patient's body has regenerated the cornea 3 to 4 times, suggesting there may be some scientific merit to this model assumption. The committee accepted the assumption about long-term success in the model, but agreed that this was subject to a high level of uncertainty that could increase the incremental cost-effectiveness ratio (ICER).

Model parameters

4.11 The committee noted that the clinical-effectiveness assumptions in the model were taken from HLSTM01 for Holoclar, and from the literature for the comparators. For Holoclar, the committee had previously heard that the estimated transplant success rates were plausible (section 4.7). However, for the comparators, the committee noted that the company had pooled the data, despite the company and ERG agreeing that pooling these data would not be appropriate (section 4.5). The company had presented a limited exploration of different success rates for the comparators, but these scenarios included changes in other assumptions and so did not explore the effect of this rate change alone. Furthermore, only 1 alternative rate for each comparator had been explored. The committee agreed that it would have been more useful to explore a range of different success rates (between 50% and 80%) because there was no comparative evidence for Holoclar and the clinical experts considered the comparator success rates to be overestimated. The committee concluded that there was a substantial level of uncertainty in the clinical-effectiveness assumptions in the company's model.

Utility values

4.12 The committee was aware that conjunctival limbal autograft needs a substantial amount of tissue from the donor eye. It queried whether the potentially negative effect on the donor eye had been captured, and heard from the company, ERG and clinical experts that it had not. The committee agreed it would have preferred to have seen analyses

including the effect on the donor eye. Moreover, the committee noted that the utility values used in the model were extraordinarily low; the values were far lower than any used in previous appraisals for eye treatments, with some lower than those for people in the last 3 months of life having palliative treatment for various cancers. The committee noted that the main reason for these low values appeared to be the utility decrement of 0.318 applied to patients experiencing disfigurement. This was over 100-times higher than the utility decrement applied to people experiencing any pain, burning or photophobia (the highest decrement was 0.019). The committee asked the clinical experts about the plausibility of these values. The clinical experts found the low overall utility difficult to quantify, but stated that LSCD has a long-term substantial negative effect on quality of life. For the high utility decrement for disfigurement, the committee heard varied reports about the relative importance of disfigurement. The clinical experts stated that for people with unilateral disease, contrary to conventional wisdom, visual acuity was not the most important outcome: because of its lasting and significant effect on their day-to-day lives, these people often prioritise disfigurement. For people with bilateral disease, disfigurement would be less of a priority than visual acuity because of the risk of complete loss of sight. The committee agreed that it was difficult to resolve this inconsistency in the relative importance of disfigurement. Furthermore, this was not the approach taken in the model, with utility values applying equally irrespective of whether disease was unilateral or bilateral. The committee agreed that the utility values used were implausibly low, noting that the ERG had used alternative values. For visual acuity, the ERG used a more plausible maximum value of 0.840 (rather than the company's assumption of 0.706). For disfigurement, it used a decrement of 0.140 (rather than the company's assumption of 0.318), using cataracts as a proxy. The committee concluded that uncertainty remained in the utility values, but the ERG values were a far more realistic reflection of the impact on quality of life.

Resource use and costs

4.13 The committee noted that the cost of autologous serum eye drops were a substantial driver of cost-effectiveness results in the model. The company had assumed in the model that patients having the comparators needed these drops after treatment and for flare-ups, but patients having Holoclar did not. The committee heard from the clinical experts that autologous serum eye drops are essential after treatment with the comparators, but less so with Holoclar because the stem cells are cultivated in a laboratory and not on the patient's eye. However, some clinicians may still choose to use them with Holoclar. The clinical experts also stated that drops would rarely be used for flare-ups because they take up to 6 weeks to prepare. Although alternative eye drops are available that would be ready for immediate use (allogenic serum eye drops), the committee heard from the ERG that using these drops would not make much difference to the model results because they were similarly priced. The committee agreed that the costs of eye drops for Holoclar had been underestimated in the model, but that the effect of this was difficult to quantify. It also agreed that eye drops after treatment were more necessary for the comparators than for Holoclar. It therefore concluded that it could cautiously accept the company's assumptions about eye drops, but remained aware that any increase in the use of eye drops would make Holoclar less cost-effective.

Cost-effectiveness results and conclusions

4.14 The committee considered the estimates of cost effectiveness calculated by the company. The base-case results were:

- Conjunctival limbal autograft dominated (that is, was both less costly and more effective than) all treatments including Holoclar in both models.
- The ICERs for Holoclar compared with conjunctival limbal allograft from a living, related donor were £7,185 per quality-adjusted life year (QALY) gained in the 1-eye treatment model, and £12,438 per QALY gained in the 2-eye treatment model.

- The ICERs for Holoclar compared with keratolimbal allograft were £2,255 per QALY gained in the 1-eye treatment model and £6,533 per QALY gained in the 2-eye treatment model.
- Holoclar dominated best supportive care in both models.

None of these ICERs took into account the committee's preferred assumptions about utility values (section 4.12) and discount rate (section 4.9). However, the ERG had presented scenarios using both of these assumptions. In these scenarios, the ICERs became less favourable:

- Conjunctival limbal autograft remained dominant in the 1-eye treatment model (the ERG did not compare Holoclar with conjunctival limbal autograft in the 2-eye treatment model).
- The ICERs for Holoclar compared with conjunctival limbal allograft from a living, related donor were £42,139 per QALY gained in the 1-eye treatment model, and £63,047 per QALY gained in the 2-eye treatment model.
- The ICERs for Holoclar compared with keratolimbal allograft were £30,415 per QALY gained in the 1-eye treatment model and £69,455 per QALY gained in the 2-eye treatment model.
- The ICERs for Holoclar compared with best supportive care were £6,948 per QALY gained in the 1-eye treatment model and £12,669 per QALY gained in the 2-eye treatment model.

Using the committee's preferred assumptions, Holoclar did not demonstrate cost effectiveness compared with either conjunctival limbal autograft or conjunctival limbal allograft from a living, related donor for treating 1 or both eyes, or keratolimbal allograft for treating both eyes. In addition, there were uncertainties in the assumptions about Holoclar's long-term success rates (section 4.10) and the use of eye drops (section 4.13) that had the potential to increase the ICERs. The committee noted that the ICER for Holoclar compared with keratolimbal allograft in the 1-eye treatment model (£30,415 per QALY gained) was marginally above

the maximum acceptable ICER of £30,000 per QALY gained. However, given the patient need (section 4.1) and innovative nature of the treatment (section 4.16), the committee agreed that it would pragmatically accept this as a demonstration of cost effectiveness. The committee therefore concluded that it could recommend Holoclar as a cost-effective use of NHS resources in people with moderate to severe LSCD after eye burns only if:

- only 1 eye is treated and
- they have already had a conjunctival limbal allograft from a living, related donor and/or a conjunctival limbal autograft when 1 eye is affected, or
- they have already had a conjunctival limbal allograft when both eyes are affected.

4.15 The committee noted that Holoclar was only cost effective for treating 1 eye. It recalled that there was almost no evidence concerning Holoclar's clinical effectiveness for treating both eyes, and agreed that it could not recommend Holoclar to treat both eyes. However, it agreed that its recommendations for treating a single eye should apply equally to unilateral and bilateral disease.

Innovation

4.16 The committee considered the innovative nature of the technology. It noted that the company had won the UK Prix Galien Orphan Product award for innovation and research. In addition, the European Medicines Agency had recognised Holoclar as the first approved stem cell medicine in Europe. The committee also agreed that the company had presented evidence to show that it offered several advantages over existing treatments. Taking all of this into account, the committee concluded that Holoclar could be considered innovative. It also agreed that most benefits of treatment with Holoclar were likely to have been captured in the QALY calculation.

4.17 Because Holoclar is a regenerative technology for an ultra-orphan condition, the company argued that the modelling was more challenging and suggested that the standard NICE reference case may be inappropriate. However, the committee was aware that NICE had worked in collaboration with the Centre for Reviews and Dissemination and Centre for Health Economics, University of York, which produced an extensive [independent report](#). This report looked at the appraisals methods and whether they are fit for purpose for regenerative medicines and cell therapies, and it found that the appraisal methods and decision framework was applicable to these treatments. The committee concluded that the standard NICE reference case was appropriate for appraising this treatment.

Summary of appraisal committee’s key conclusions

TAXXX	Appraisal title:	Section
Key conclusion		
Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells) is recommended as an option in people with moderate to severe limbal stem cell deficiency (defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity) after eye burns, only if: <ul style="list-style-type: none"> • only 1 eye is treated and • they have already had a conjunctival limbal allograft from a living, related donor and/or a conjunctival limbal autograft when 1 eye is affected, or • they have already had a conjunctival limbal allograft when both eyes are affected and • the company provides it with the discount agreed in the patient access scheme. 		1.1; 1.2

<p>Using the committee’s preferred assumptions, Holoclar did not demonstrate cost effectiveness compared with either conjunctival limbal autograft or conjunctival limbal allograft from a living, related donor for treating 1 or both eyes, or keratolimbal allograft for treating both eyes. The committee noted that the most plausible ICER for Holoclar compared with keratolimbal allograft in the 1-eye treatment model (£30,415 per QALY gained) was marginally above the maximum acceptable ICER of £30,000 per QALY gained. However, given the patient need and innovative nature of the treatment, the committee agreed that it would pragmatically accept this as a demonstration of cost effectiveness in the circumstances outlined in the recommendation.</p>		<p>4.14 to 4.15</p>
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The committee heard from the clinical experts that LSCD can be life-changing: in addition to visual impairment, the condition is associated with high levels of pain and photophobia and represents a major psychological burden. The committee agreed that LSCD can be a life-changing and severely debilitating condition.</p>	<p>4.1</p>
<p>The technology</p>		

Proposed benefits of the technology	The committee recognised that patients would greatly value a new treatment which successfully treated LSCD, particularly if it reduced the need for external donors and damage to the donor eye.	4.2 to 4.3
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee noted that the company had won the UK Prix Galien Orphan Product award for innovation and research. In addition, the European Medicines Agency had recognised Holoclar as the first approved stem cell medicine in Europe. The committee concluded that Holoclar could be considered innovative.	4.16 to 4.17
What is the position of the treatment in the pathway of care for the condition?	The committee heard that supportive care treatments would be offered and conservative surgery such as corneal scraping may also be offered before attempting limbal stem cell transplantation.	4.2
Adverse reactions	The committee heard from the clinical experts that Holoclar needs a smaller amount of tissue than conjunctival limbal autograft. The smaller biopsy means a much lower risk of damage to the donor eye.	4.4 4.12
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee noted that the evidence for Holoclar (studies HLSTM01, HLSTM03 and HLSTM04) and the comparators was mostly from case series. It noted that these studies offer poorer quality evidence, because they do	4.5

	not contain a comparison group. The comparator evidence consisted of 23 smaller studies with high levels of heterogeneity, which the company, ERG and committee agreed made them unsuitable for data pooling. The committee also noted that the clinical evidence for Holoclar was limited to treating 1 eye only.	
Relevance to general clinical practice in the NHS	The clinical experts stated that the results for Holoclar were plausible, but that the results for the comparators should be interpreted with more caution. In the absence of stronger evidence in this disease area, the committee accepted this clinical evidence for its decision-making.	4.5
Uncertainties generated by the evidence	No clinical evidence had been presented for using Holoclar in more than 1 eye.	4.5
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that it would differentiate between the treatment of 1 or 2 eyes. No clinical evidence had been presented for using Holoclar in more than 1 eye.	4.5, 4.15
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The results from HLSTM01 showed that 72.1% of patients had a successful Holoclar transplant. For the comparators, transplant success varied between 60.0% and 100.0%. There were no direct comparative studies.	4.5, 4.7

Evidence for cost effectiveness		
Availability and nature of evidence	The company presented 2 separate models: a 'unilateral' and a 'bilateral' model. The models were similar, with both consisting of a decision tree followed by a Markov model, but the bilateral model assumed that patients had treatment in both eyes. The committee agreed that it would be more informative to consider the company's unilateral model as the '1-eye treatment' model and the bilateral model as the '2-eye treatment' model.	4.8
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The committee noted that:</p> <ul style="list-style-type: none"> • the assumption of long-term success was subject to a high level of uncertainty but accepted this assumption; • the company had pooled the comparator data despite the company and ERG agreeing that pooling these data would not be appropriate; • uncertainty remained in the utility values, but the ERG values were more realistic than the company value; • the costs of eye drops for Holoclar had been underestimated in the model, but that the effect of this was difficult to quantify. 	4.10 to 4.13

<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 heard that the potentially negative effect on the donor eye had not been captured.</p>	<p>4.12</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The committee noted that Holoclar was more cost-effective when treating 1 eye compared with 2 eyes.</p>	<p>4.14</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee understood that long-term success, success rate and utility values had an impact on the incremental cost-effectiveness ratio.</p>	<p>4.10, 4.11, 4.12</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<ul style="list-style-type: none"> • Conjunctival limbal autograft remained dominant in the 1-eye treatment model (the ERG did not compare Holoclar with conjunctival limbal autograft in the 2-eye treatment model). • The ICERs for Holoclar compared with conjunctival limbal allograft from a living, related donor were £42,139 per QALY gained in the 1-eye treatment model, and £63,047 per QALY gained in the 2-eye treatment model. • The ICERs for Holoclar compared with keratolimbal allograft were £30,415 per QALY gained in the 1-eye treatment model and £69,455 per QALY gained in the 2-eye treatment model. • The ICERs for Holoclar compared with best supportive care were £6,948 per QALY gained in the 1-eye treatment model and £12,669 per QALY gained in the 2-eye treatment model. 	<p>4.14</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>In its submission the company reiterated a concern raised during scoping that a negative recommendation could disproportionately affect military personnel. However, this was not considered an equalities issue because:</p> <p>1) The disability is a consequence of the condition.</p> <p>2) The Committee’s recommendations do not exclude or impact differently on any populations.</p>	<p>-</p>
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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 limbal stem cell deficiency after eye burns and the doctor responsible for their care thinks that Holoclar is the right

treatment, it should be available for use, in line with NICE's recommendations.

- 5.4 The Department of Health and Chiesi Pharmaceuti have agreed that Holoclar will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to **[NICE to add details at time of publication]**

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
April 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.

Irina Voicechovskaja

Technical lead

Carl Prescott, Alexandra Filby

Technical adviser

Stephanie Yates

Project manager

ISBN: **[to be added at publication]**