

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Ex vivo expanded autologous human corneal epithelial cells for treating moderate to severe limbal stem cell deficiency due to ocular burns

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ex vivo expanded autologous human corneal epithelial cells containing stem cells within its marketing authorisation for treating moderate to severe limbal stem cell deficiency due to ocular burns.

Background

The cornea is the clear, rigid layer covering the front of the eye and it is divided in 4 quadrants: superior, temporal, inferior and nasal. Cells on the cornea surface are constantly being renewed and replaced by limbal stem cells which are located in the ocular surface between the cornea and the bulbar conjunctiva. An injury to the source of the limbal stem cells can cause a deficiency of these cells known as limbal stem deficiency (LSCD), reducing the renewal and replacement of the surface of the cornea. This results in the cornea being repaired by different types of eye cell and excessive ingrowth of blood vessels (neovascularisation), which can make the cornea opaque and impair vision. Ocular burns because of chemicals or heat can damage these stem cells. Moderate to severe LSCD is defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity.

The estimated prevalence of LSCD due to ocular burns in Europe is 0.3 in 10,000 people¹, which is equivalent to about 1800 people in England. In 2014/15, there were approximately 3600 corneal transplants for a variety of indications in the UK². The number of corneal transplants for ocular surface burns is thought to be very small. The estimated incidence of severe chemical corneal injury in the UK is 0.02 in 100,000 people³.

The aim of treatment is to restore a healthy conjunctival and corneal surface. Simple treatments include topical steroids, ocular lubricants, bandage contact lenses and autologous serum eye drops. Historically, LSCD has been treated with surgical procedures based on tissue therapy. Tissue from the healthy eye has been used for conjunctival limbal autografts for people with unilateral LSCD, and tissue from a cadaver or a relative donor has been used for limbal epithelial stem cells allografts for bilateral disease. However these procedures are associated with a high risk of allograft rejection and damage to the healthy eye. There are no specific treatments available for treating LSCD due to physical or chemical ocular burns.

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 corneal surface. It consists of cells taken from the patient's limbus (at the edge of the cornea) and then grown in a laboratory and frozen until the date of surgery is confirmed. The cells are grown on a membrane made of a protein called fibrin and the final product is then sent back to the hospital, where it is immediately surgically implanted in the patient's eye.

Ex vivo expanded autologous human corneal epithelial cells containing stem cells has a conditional marketing authorisation in the UK for 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. A minimum of 1 - 2 mm² of undamaged limbus is required for biopsy. As part of the conditional marketing authorisation the company is conducting a prospective, open-label, uncontrolled interventional study to assess the efficacy and safety of autologous cultivated limbal stem cells grafting for restoration of corneal epithelium in patients with limbal stem cell deficiency due to ocular burns.

Intervention(s)	Ex vivo expanded autologous human corneal epithelial cells containing stem cells
Population(s)	Adults 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 and a minimum of 1 - 2 mm ² of undamaged limbus
Comparators	<p>For people with unilateral limbal stem cell deficiency:</p> <ul style="list-style-type: none"> • conjunctival limbal autograft • best supportive care <p>For people with bilateral limbal stem cell deficiency:</p> <ul style="list-style-type: none"> • limbal epithelial stem cells allografts • best supportive care

Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • clinical parameters of limbal stem cell deficiency including stability and transparency of the corneal epithelium and superficial corneal neovascularisation • symptoms of limbal stem cell deficiency including pain, burning and photophobia • visual acuity (the affected eye) • visual acuity (the whole person) • adverse effects of treatment • health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.</p>
Other considerations	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
Related NICE recommendations and NICE Pathways	<p>Related Interventional Procedures:</p> <p>'Corneal endothelial transplantation' (2009) NICE interventional procedures guidance 304</p> <p>'Tissue-cultured limbal stem cell allograft transplantation for regrowth of corneal epithelium' (2007) NICE interventional procedures guidance 216</p> <p>Related NICE Pathways:</p> <p>Eye conditions (2015) NICE pathway.</p> <p>http://pathways.nice.org.uk/pathways/eye-conditions</p>

Related National Policy	<p>Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 3, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf</p> <p>NHS England (2014) Manual for prescribed specialised services 2013/14. Chapter 12. D12 - Adult specialist ophthalmology services.</p> <p>NHS England (2013) NHS standard contract for specialised ophthalmology (adult). Schedule 2 - the services - A. the specifications.</p> <p>NHS England (2013) 2013/14 NHS standard contract for osteo-odonto-keratoprosthesis service for corneal blindness (adults). particulars, schedule 2- the services, a- service specification</p>
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Questions for consultation

Have all relevant comparators for Holoclar been included in the scope? Which treatments are considered to be established clinical practice in the NHS for moderate to severe limbal stem cell deficiency due to ocular burns? Is corneal transplant a treatment option? How should best supportive care be defined? Are there any subgroups of people in whom Holoclar is expected to be more clinically effective and cost effective or other groups that should be examined separately?

What is the estimated number of patients with limbal stem cell deficiency due to ocular burns in England?

Where do you consider Holoclar will fit into the existing NICE pathway, [Eye conditions](#)?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which Holoclar is licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider Holoclar to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of Holoclar can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at <http://www.nice.org.uk/article/pmg19/chapter/1-Introduction>)

References

1. European Medicines Agency (2015) [Public summary of opinion on orphan designation](#). Accessed July 2015.
2. NHS Blood and Transplant (2015) [Organ Donation and Transplantation Activity figures for the UK](#). Accessed July 2015
3. Macdonald ECA, Cauchi PA, Azuara-Blanco A et al. (2009) Surveillance of severe chemical corneal injuries in the UK. *British Journal of Ophthalmology*, 93: 1177-1180.